

endothelial activation and result in increased surface expression of cell adhesion molecules (CAMs), such as P-selectin, E-selectin, and intracellular CAM (ICAM), thereby promoting the adhesion and activation of leukocytes as well as platelets,<sup>9</sup> and can lead to pathological thrombosis. Clinically, soluble P-selectin, in combination with Wells' score and D-dimer, has a high sensitivity and specificity for the diagnosis of DVT.<sup>10,11</sup>

## Venous Biomechanics

Veins allow a very large volume capacitance and tonal regulation to rapidly redistribute overall blood volume. Approximately 60% to 80% of circulating blood is stored in the venules and systemic veins at any given time. The function of the blood capacitance system via vasoregulation is to maintain the filling of the heart as well as to compensate for orthostatic changes. The physiology of venous blood flow in the limb related to the calf muscle pump and other actions is detailed in Chapter 24 (Vascular Laboratory: Venous Physiologic Assessment).

Everyday activities and changes in body position cause large changes in venous pressure. The average venous pressure at the foot is approximately 100 mm Hg in a person 5 feet 10 inches (1.78 m) tall weighing 75 kg. This pressure drops significantly with ambulation and during recumbence. The venous valves are endothelium-lined folds of tunica intima that allow unidirectional flow, contribute to this pressure reduction, and maintain prograde blood flow. To accommodate pressure and volume changes, veins undergo complex alterations in shape, depending on the blood volume, resistance, and the amount of blood flow within the system. Less vascular resistance occurs with a circular shape than an elliptical shape, and thus as venous volume increases, resistance to flow lessens.

Unlike arteries, large veins lack an extensive elastic lamella (composed of elastin) but exhibit marked distensible properties. Veins have a much smaller ratio of wall thickness to radius and higher incremental distensibility in the low-pressure range than arteries, thus indicating that the elastic modulus of veins can greatly exceed the stress modulus of arteries. As a result, veins have a high breaking pressure, nearly four atmospheres.<sup>12</sup> Much of the stress-bearing function of the vein wall may depend on its smooth muscle cell and elastin content, in contrast to the abundance of collagen in the arterial wall. Indeed, vein wall compliance is decreased after experimental venous thrombosis (VT) injury, which correlates with its increased collagen content,<sup>13</sup> and disrupted elastin, as measured histologically.<sup>14</sup>

## DEEP VENOUS THROMBOSIS

Venous thromboembolism (VTE) is a significant healthcare problem in the United States, with an estimated 900,000 cases of VT and pulmonary embolism (PE), causing approximately 300,000 deaths yearly.<sup>15</sup> For the past 150 years, understanding the pathogenesis of VTE has centered on Virchow's triad of stasis, changes in the vessel wall (now recognized as injury), and thrombogenic changes in the blood. Stasis is probably permissive, and not a direct cause, whereas systemic infection and systemic inflammation may be more causal than previously thought.<sup>16,17</sup>

## Venous Thrombosis Pathways

### Coagulation Cascade

Hemostasis is typically initiated by damage to the vessel wall and disruption of the endothelium, although it may be initiated in the absence of vessel wall damage, particularly in VT.<sup>18</sup> Vessel wall damage simultaneously results in release of TF, a cell membrane protein, from injured cells and circulating blood, with subsequent activation of the extrinsic pathway of the coagulation cascade. These two events are critical to the activation and acceleration of thrombosis (Fig. 9.1). Differences in local organ mechanisms may cause region-specific susceptibility to thrombosis. For example, hemostasis in cardiac muscle may be more dependent on the extrinsic pathway for thrombosis, whereas skeletal muscle may be more dependent on the intrinsic pathway for thrombosis.<sup>19</sup>

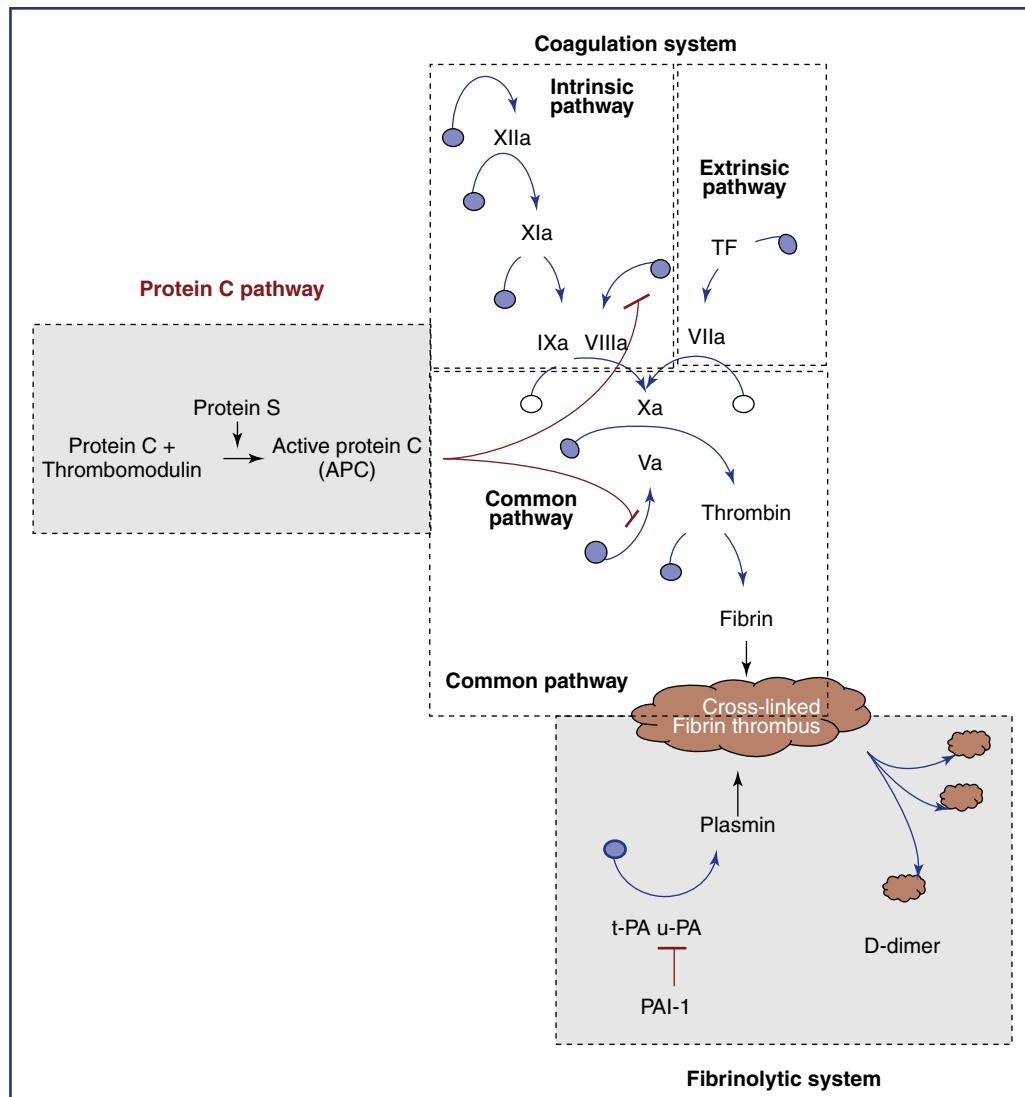
Coagulation can be activated through the intrinsic pathway with activation of factor XI to XIa, which subsequently converts factor IX to IXa and promotes formation of the Xase complex and ultimately thrombin. Another mechanism by which this occurs *in vitro* is through the contact activation system, whereby factor XII (Hageman factor) is activated to XIIa when complexed to prekallikrein and high-molecular-weight kininogen (HMWK) on a negatively charged surface; factor XIIa then activates factor XI to XIa. Both thrombin and factor XIa are also capable of activating factor XI.<sup>20</sup>

Thrombin (factor II) is central to coagulation through its action of cleavage and release of fibrinopeptide A (FPA) from the  $\alpha$  chain of fibrinogen and fibrinopeptide B (FPB) from the  $\beta$  chain of fibrinogen. This causes fibrin monomer polymerization and cross-linking, which stabilizes the thrombus and the initial platelet plug. Thrombin also activates factor XIII to XIIIa, which catalyzes the cross-linking of fibrin as well as that of other plasma proteins, such as fibronectin and  $\alpha_2$ -antitrypsin, resulting in their incorporation into the thrombus and increasing resistance to thrombolysis.<sup>21</sup> In addition, factor XIIIa activates platelets as well as factors V and VIII, further amplifying thrombin production.

### Platelets

Platelet activation and the formation of an effective hemostatic "platelet plug" is a primary thrombotic event, extensively studied in both arterial thrombosis and VT. Two platelet activation routes are thought to exist physiologically.<sup>22</sup> Without direct vessel damage, platelet activation may occur via TF de-encryption and activation by protein disulfide isomerase, with factor VIIa generation and activation of platelets. Alternatively, subendothelial collagen may directly bind to glycoprotein (GP) VI and vWF, leading to platelet capture and activation.

Platelet interactions and activation are mediated by vWF, whose receptor is GPIb, via GPIIb/IIIa to fibrin.<sup>23</sup> Activation of platelets leads to the release of the prothrombotic contents of platelet granules, which contain receptors for coagulation factors Va and VIIIa. In addition, platelet activation also leads to the elaboration of arachidonic acid metabolites such as thromboxane A<sub>2</sub>, further promoting platelet aggregation



**Figure 9.1** Integrated representation of the coagulation cascade and the main players for the intrinsic, extrinsic and common pathways, the natural anticoagulant protein C pathway and the fibrinolytic system with the degradation product D-dimer. *PAI-1*, plasminogen activator inhibitor-1; *TF*, tissue factor; *tPA*, tissue plasminogen activator; *uPA*, urokinase-type plasminogen activator.

(as well as vasoconstriction). Changes in platelet shape result in exposure of negatively charged procoagulant phospholipids normally located within the inner leaflet of the platelet membrane.<sup>24</sup> Platelets also release microparticles (MPs), rich in TF and other procoagulants, which accelerate and concentrate the thrombus generation. Interestingly, circulating TF may be more important in venous thrombosis than in arterial thrombosis.<sup>18,25</sup>

## Natural Anticoagulants

Several interrelated processes localize thrombotic activity to sites of vascular injury. First, anti-thrombin (AT) is a central anticoagulant protein that binds to thrombin and interferes with coagulation by three major mechanisms: (1) inhibition of thrombin prevents removal of fibrinopeptides A and B from fibrinogen, limiting fibrin formation; (2) thrombin becomes unavailable for activation of factors V and VIII, thus slowing the coagulation cascade; and (3) thrombin-mediated platelet activation and aggregation are inhibited. In the presence

of heparin, the accelerated inhibition of thrombin by anti-thrombin results in systemic anticoagulation. Anti-thrombin has been shown to directly inhibit factors VIIa, IXa, Xa, XIa, and XIIa. Thus, patients with a genetic deficiency of AT are at much higher risk for development of VTE than the normal population.

A second natural anticoagulant is activated protein C (APC), which is produced on the surface of intact endothelium when thrombin binds to its receptor, thrombomodulin, and endothelial protein C receptor (EPCR). The thrombin–thrombomodulin complex inhibits the actions of thrombin and also activates protein C to APC. APC, in the presence of its cofactor protein S, inactivates factors Va and VIIIa, therefore reducing Xa and prothrombinase activity (see Fig. 9.1).<sup>26</sup>

The third innate anticoagulant is TFPI. This protein binds the TF-VIIa complex, thus inhibiting the activation of factor X to Xa and formation of the prothrombinase complex. Interestingly, factor IX activation is not inhibited. Finally, heparin cofactor II is another inhibitor of thrombin whose action is in the extravascular compartment. The activity of heparin cofactor II

is augmented by glycosaminoglycans, including both heparin and dermatan sulfate, but its deficiency is not associated with increased VTE risk.<sup>27</sup>

## Thrombolysis

Physiologic thrombus formation is balanced by localized thrombolysis to prevent pathologic intravascular thrombosis. Plasmin, the central fibrinolytic enzyme, is a serine protease generated by the proteolytic cleavage of the proenzyme plasminogen. Its main substrates include fibrin, fibrinogen, and other coagulation factors. Plasmin also interferes with vWF-mediated platelet adhesion by proteolysis of GPIb.<sup>28</sup>

Activation of plasminogen occurs through several mechanisms. In the presence of thrombin, vascular endothelial cells produce and release tPA as well as  $\alpha_2$ -antiplasmin, a natural inhibitor of excess fibrin-bound plasmin (see Fig. 9.1). As a thrombus is formed, plasminogen, tPA, and  $\alpha_2$ -antiplasmin become incorporated into it. In contrast to free circulating tPA, fibrin-bound tPA is an efficient activator of plasminogen. A second endogenous activator of plasminogen is through the uPA, also produced by endothelial cells but with less affinity for fibrin. Activation of uPA *in vivo* is not completely understood. However, it is hypothesized that plasmin in small amounts (produced through tPA) activates uPA, leading to further plasminogen activation and amplification of fibrinolysis.<sup>29</sup>

The third mechanism of plasminogen activation involves factors of the contact activation system; activated forms of factor XII, kallikrein, and factor XI can each independently convert plasminogen to plasmin. These activated factors may also catalyze the release of bradykinin from high-molecular-weight kininogen, which further augments tPA secretion. Finally, APC has been found to proteolytically inactivate plasminogen activator inhibitor type 1 (PAI-1), an inhibitor of plasmin activators that is released by endothelial cells in the presence of thrombin.<sup>30</sup>

The degradation of fibrin polymers by plasmin ultimately results in the creation of fragment E and two molecules of fragment D, which are released as a covalently linked dimer (D-dimer).<sup>31</sup> Detection of D-dimer in the circulation is a marker for ongoing thrombus metabolism and has been shown to accurately predict ongoing risk of recurrent VTE.<sup>32</sup> Interestingly, the resting state of the fibrinolytic system within the vein wall is lower in the area of the valvular cusps, and is affected by aging.<sup>33,34</sup> In comparison with other anatomic locations, the deep veins of the lower limb have the lowest fibrinolytic activity in soleal sinuses as well as in the popliteal and femoral vein regions. This observation underlies a popular hypothesis as to why DVT most commonly originates in the lower limb.

## Plasminogen Inhibitors and Thrombosis

Activation of plasminogen provides localized proteolytic activity,<sup>35–37</sup> and in plasma, PAI-1 is the primary inhibitor of plasminogen activators. It is secreted in an active form from liver and endothelial cells and is stabilized by binding to vitronectin

(and inhibits thrombin in this form). PAI-1 is stored in the alpha-granules of quiescent platelets.<sup>38</sup> PAI-1 levels are elevated by hyperlipidemia, and PAI-1 elevation appears to synergize with factor V Leiden genetic abnormalities.

Studies on the role of elevated PAI-1 in VT have been contradictory,<sup>39,40</sup> although it is plausible that elevated PAI-1 could suppress fibrinolysis and increase thrombosis potential. In humans, genetic polymorphisms correlate with increased risk of VTE. The highest levels of PAI-1 have been noted in those individuals carrying the 4G/4G polymorphism. Studies have found an eightfold higher risk for VTE in patients with the 4G allele in combination with other thrombophilic markers,<sup>41</sup> and a 4.5-fold higher risk for PE in patients with 4G/4G polymorphism and protein S deficiency.<sup>42</sup>

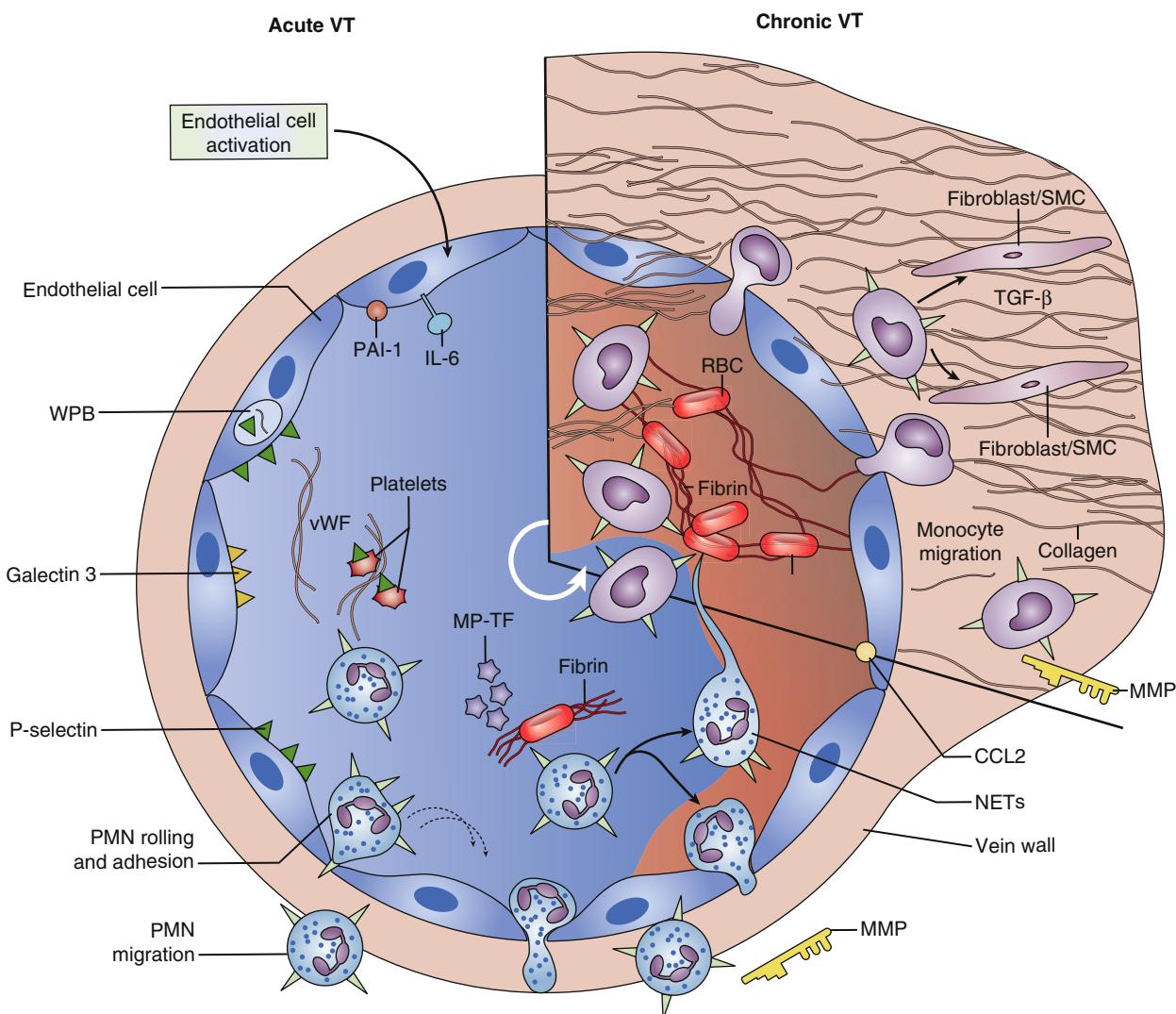
## Inflammation and Thrombosis

The relationship between thrombosis and inflammation was first suggested in the early 1970s.<sup>43</sup> Inflammation increases cell adhesion molecule expression (CAM), TF, membrane phospholipids, fibrinogen, and the reactivity of platelets while decreasing thrombomodulin and inhibiting fibrinolysis (Fig. 9.2).<sup>44</sup>

Selectins are CAMs that are involved with early VT genesis and may be involved with vein wall injury. Selectin inhibition, such as P-selectin inhibition, is associated with decreased vein fibrosis experimentally in rats, as well in primates.<sup>45,46</sup> In mice genetically deleted for E-selectin, P-selectin, and E-/P-selectin together, showed a significant correlation in decreased fibrin deposition and decreased thrombus mass in a stasis VT model.<sup>47</sup> Exogenous inhibition of P-selectin via rPSGL-1 was also associated with smaller thrombi in a rat model.<sup>48</sup> Similarly, exogenous E-selectin inhibition is effective at inhibiting thrombus formation, without attendant bleeding risks.<sup>49</sup> These CAM targets are also being investigated clinically for anti-thrombotic therapy.

Microparticles are small (<1  $\mu\text{m}$ ) phospholipid vesicles which are shed from platelets, leukocytes, and endothelial cells in a calcium-dependent fashion, and are involved in the initiation and amplification of thrombosis.<sup>50</sup> These microparticles add to the growing thrombus via interactions between P-selectin and its receptor, P-selectin glycoprotein ligand-1 (PSGL-1). Microparticles lack DNA and RNA, but subpopulations of microparticles rich in TF and phosphatidylserine have been identified.<sup>51</sup> Fusion of microparticles with activated platelets results in decryption of TF and the initiation of thrombosis.<sup>52</sup> These vesicles have direct exogenous procoagulant activity, as shown by normalization of tail bleeding times in hemophilic mice.<sup>53</sup> Moreover, microparticles shed from platelets express PAI-1. In this manner, platelet microparticles not only are prothrombotic but also inhibit fibrinolysis, facilitating thrombus growth.<sup>54</sup> The results of these studies provide evidence that microparticles are associated with VT, and also their potential role as biomarkers for DVT.<sup>55</sup>

Galectin 3 (gal3) and galectin 3 binding protein (gal3bp) appears to play a role in human DVT, as suggested by the presence in microparticles collected from human patients diagnosed with DVT.<sup>56</sup> Gal3bp is a member of the lectin family,



**Figure 9.2** Schematic representation of the inflammatory events during acute and chronic venous thrombosis in an anticlockwise fashion. The initial inflammatory events involve endothelial activation with secretion of cytokines, PAI-1 and release of vWF and P-selectin. This platform favors PMN recruitment. Platelet activation also contributes to the initial steps and the fibrin RBC rich thrombus (in light red) forms. Vein wall, in beige, increases thickness over time. CCL2, C-C motif ligand 2; IL-6, interleukin-6; MMP, matrix metalloproteinase; MP-TF, microparticle tissue factor; NETs, neutrophil extracellular traps; PAI-1, plasminogen activator-1; PMN, polymorphonuclear; RBC, red blood cell; TGF- $\beta$ , transforming growth factor-beta; VT, venous thrombosis; vWF, von Willebrand factor; WPB, Weibel-Palade Body.

associated with integrin-mediated cell adhesion.<sup>57</sup> Recently, gal3 and gal3bp were discovered to be associated with murine thrombogenesis.<sup>55</sup> In addition, gal3 could be a potential biomarker in patients with acute DVT, as increased circulating gal3bp and gal3 was observed during VT conditions in both mice and humans.

### Thrombus Resolution and Vein Wall Remodeling

Regardless of the location and extent of acute DVT, the resolution process is complex.<sup>58</sup> In humans, the natural fibrinolytic mechanisms break down the thrombus over time at variable rates.<sup>59</sup> Resolution of experimental VT resembles wound

healing, involving profibrotic growth factors, collagen deposition, and activation of matrix metalloproteinase (MMP) (see Fig. 9.2). The fact that leukocytes invade the thrombus in a specific sequence suggests their importance in normal thrombus resolution.<sup>60</sup> Real-time *in vivo* imaging has also shown that leukocyte concentration and MMP activity colocalize to areas of recanalization.<sup>61,62</sup>

The first leukocyte sub-type arriving to the thrombus is the polymorphonuclear neutrophil (PMN). Although PMNs may cause vein wall injury, they contribute to both early thrombus amplification and early thrombus resolution. The role of PMNs in promoting early DVT by release of neutrophil extracellular traps (NETs) has been shown in primate and murine models of thrombosis.<sup>63</sup> Inflammatory activation of PMNs causes

degranulation of nucleic DNA, which is complexed with antimicrobial peptides and allows platelets and coagulation factors to assemble in juxtaposition to the vein wall. Consistently, DNase treatment can directly accelerate venous thrombosis resolution.<sup>64</sup>

The monocyte/macrophage (Mo/MΦ) is likely the most important cell for later DVT resolution.<sup>60</sup> In mice, monocyte influx into the thrombus correlates with elevations of monocyte chemotactic protein-1 (MCP-1), one of the primary CC chemokines that direct monocyte chemotaxis and activation;<sup>65,66</sup> MCP-1 has also been associated with DVT resolution.<sup>67</sup> Targeted deletion of CC receptor-2 (CCR-2 KO) in the mouse model of stasis thrombosis is associated with late impairment of thrombus resolution, probably via impaired interferon- $\gamma$ -inducible proteinase activity, which may be independent of Mo/MΦ.<sup>68</sup>

However, Mo/MΦ are not required for early stasis or non-stasis thrombogenesis, as suggested from a conditional Mo/MΦ (CD11b-DTr) conditional depletion model.<sup>69</sup> A recent study in a non-stasis thrombosis model showed that Mo/MΦ peak by 6 to 10 days.<sup>70</sup> Utilizing a lysM<sup>+</sup> leukocyte conditional depletion strategy, thrombosis resolution was enhanced when this cell line was depleted, with decreased PMNs and increased IL-4 and IL-10, suggesting a shift to a pro-healing response. To further investigate this, Tbx21<sup>-/-</sup> mice, lacking ability to produce interferon gamma (IFN- $\gamma$ ), are skewed toward a TH<sub>2</sub> immune response. Post-thrombosis, these mice had decreased thrombus collagen, increased neovascular channels, and decreased IL-12 and CCL-2 at day 14 in the same non-stasis model. Others have shown that VT resolution is accelerated with IFN- $\gamma$  deletion, and consequently increased MMP-2 and MMP-9.<sup>71</sup> The micro-environment of the VT seems to determine whether the Mo/MΦ is proinflammatory, which drives tissue damage, or pro-resolution/healing, which promotes tissue homeostasis.<sup>72-78</sup>

Compared with innate immune cells, little is known about the role of adaptive immunity in venous thrombosis. Limited data from murine studies suggest that CD4<sup>+</sup> T cells are the most common lymphocyte present in the thrombus, peaking weeks after thrombosis has occurred. Complete or partial ablation of the T-cell response disrupts Mo/MΦ recruitment to the resolving thrombus, alters the proinflammatory versus pro-healing balance, and subsequent thrombus clearance.<sup>79,80</sup> T effector memory cells undergo antigen independent activation, invade the vein wall and direct subsequent cytokine response. Their direct influence on vein wall injury remains an active area of study.

The local venous environment is by definition hypoxic. A major angiogenic growth factor is hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ). Murine stasis models of venous thrombosis have shown that thrombosis stimulates HIF-1 $\alpha$ , which thus accelerates thrombus resolution.<sup>81</sup> VEGF has also been associated with increased thrombus recanalization in smaller venous thrombi from rat models of DVT. VEGF was also correlated with higher numbers of thrombus monocytes.<sup>82</sup> Thus, thrombus resolution is in part dependent on neovascularization. The effect of mechanical stretch, such as by a venous thrombus, may also stimulate HIF-1 $\alpha$  as well as MMP-2 and MMP-9, all of which lead to reduced vein contractility.<sup>83</sup>

As the thrombus resolves, a number of proinflammatory factors are released into the local environment, including interleukin-1 $\beta$  (IL-1 $\beta$ ) and tumor necrosis factor- $\alpha$ .<sup>84</sup> The cellular sources of these different mediators have not been specifically defined but probably include leukocytes and smooth muscle-like cells within the resolving thrombus and adjacent vein wall. Leukocyte kinetics in the vein wall during DVT are similar to what is observed in the thrombus, with an early influx of PMNs followed by Mo/MΦ (see Fig. 9.2). On the basis of experimental studies, elastinolysis and collagenolysis seem to occur early, as measured by an increase in vein wall stiffness persisting through 14 days, and are accompanied by elevated MMP-2 and MMP-9 activities.<sup>13,14</sup> Genetic deletion of MMP-2 or MMP-2/9 is associated with decreased vein wall fibrosis, possibly by modulating vein wall elastin/collagen metabolism, as well as monocyte influx.<sup>85</sup> Thus, early vein wall injury is associated with active matrix remodeling that seems to promote late fibrosis, not unlike many organ responses to inflammation burnout.<sup>86</sup>

Loss of venous endothelium likely also contributes to vein wall fibrosis as well as the predisposition to recurrent thrombosis. An experimental model of DVT showed lower expression of homeostatic endothelial gene products such as NO and thrombomodulin compared to controls, which correlated with loss of vWF positive cell luminal staining.<sup>87</sup> Other investigators have found that prolonged venous stasis is associated with decreased plasminogen activators, probably related to the loss of endothelium.<sup>88</sup>

The profibrotic growth factor TGF- $\beta$  is present in the thrombus and is activated with normal thrombolysis.<sup>88</sup> TGF- $\beta$  may be a key mechanism promoting vein wall fibrosis. Late fibrosis has been observed in a mouse model of DVT, which demonstrated an increase in vein wall collagen,<sup>89</sup> specifically an increase in collagen I and III gene expression, as well as increases in MMP-2 and MMP-9 gene expression and activity.

Recurrent DVT is a strong risk factor for post-thrombotic syndrome (PTS).<sup>90</sup> A recently published model was developed that suggests the vein wall is primed for a fibrotic phenotype, with increased levels of transforming growth factor-beta (TGF- $\beta$ ), interleukin-6 (IL-6), and MMPs in the secondary (e.g. recurrent) VT post-thrombotic vein walls.<sup>91</sup> This study also delineated the incorporation of the primary thrombus into the vein wall, contributing to the thickness and architecture of the post-thrombotic vein.

## CHRONIC VENOUS INSUFFICIENCY

The common mechanism of chronic venous insufficiency (CVI) is venous reflux between the superficial and deep systems, either at the site of perforators or through other deep and superficial system connections, which accounts for the increased venous hydrostatic pressure transmitted to the superficial veins and tissues. An obstructed vein segment worsens this process, and it is well-established that DVT both directly damages valves and indirectly contributes to reflux via flow obstruction. More recently, primary CVI has been implicated as a novel risk factor for DVT development.<sup>92</sup>

Experimentally, venous hypertension activates leukocytes,<sup>93</sup> although the activation is probably a local phenomenon.<sup>94</sup> The process of vein wall fibrosis plays a contributing role in valvular damage, which then worsens the hydrostatic pressure regulation and consequently promotes greater venous hypertension while in the upright position. Molecular and cellular events seem to point to adaptive responses to injury as well as abnormal healing.

## Historical Perspective and General Background

Several important theories have been postulated regarding the etiology and pathophysiology of CVI. In 1917, John Homans<sup>95</sup> produced a clinical treatise on the diagnosis and the management of patients with CVI and coined the term “post thrombotic syndrome.” Local tissue hypoxia and alterations in nutrient blood flow were proposed as an underlying etiology by Browse and Burnand.<sup>96</sup> Their important study directly demonstrated the effect of venous hypertension on the venous microcirculation, and they observed histologically the occurrence of pericapillary fibrin deposition in large capillaries, which they called the “fibrin cuff.” Coleridge proposed that leukocyte trapping in slow-flow and distended venous segments may underlie much of CVI development.<sup>97</sup>

## Varicose Veins

Varicose veins (VVs) have been described since before the Common Era and are obvious on the lower limbs of many people. The fact that varicose veins primarily affect the lower limb directly implicates the upright nature of humans – specifically, the effect of hydrostatic pressure on the pathophysiology of such veins. The relationship between body weight and the extent/symptoms of varicose veins is variable. Limb symptoms are generally local and consist of pruritus and swelling. Occasionally, varicose veins can erode and bleed. Conversely, most such veins do not thrombose, despite relatively slow blood flow through these tortuous structures, pointing to the natural anticoagulant nature of venous endothelium even in structurally abnormal vessels.

Varicose veins are typically located in the great and small saphenous distributions and their tributaries in the superficial system.<sup>98</sup> Related risk factors are multiple, including primary etiologies associated with pregnancy, prolonged standing, female gender, and, rarely, congenital absence of valves.<sup>99</sup> In addition, varicosities may develop as a result of prior DVT or trauma. Studies support a genetic predisposition to varicose veins.<sup>100</sup> In a prospective study of 402 subjects, the risk of development of varicose veins was 90% if both parents were affected, 25% for males and 62% for females if one parent was affected, and 20% if neither parent was affected.<sup>101</sup> These data suggest an autosomal dominant with a variable penetrance mode of genetic transmission.

Varicose veins lead to matrix dysregulation with altered expressions of collagen types I and III, with varying dysregulation patterns.<sup>102</sup> The observed pathology suggests a net effect of matrix deposition. One mechanism for these changes may be local upregulation of MMPs and fibrinolytic activity within the

microenvironment.<sup>103</sup> Overall differences in MMP-9 protein have also been identified, and it is likely, with the inflammatory influx, that MMP-9 is released primarily from PMNs and may be less important than MMP-2.<sup>104</sup>

This disordered vein structure also correlates with altered vasoreactivity. The contractual response of varicose and normal great saphenous rings to various alpha-adrenergic and non-alpha-adrenergic receptors has shown decreased contractility as compared with controls.<sup>105</sup> This lower contractility may be due to repeated overdistention or impaired contractility related to persistent vein wall tension. However, the response is segmental and likely adaptive.<sup>106</sup> Defining whether varicose veins involve an initial wall defect and a secondary hemodynamic factor or vice versa is still under debate.<sup>107</sup>

## Pathophysiology of Stasis Dermatitis and Dermal Fibrosis

Stasis venous dermatitis is a disease of chronic dermal inflammation due to persistent and sustained cutaneous and dermal injury secondary to venous hypertension. The primary injury may be extravasation of macromolecules and red blood cell products into the dermal interstitium, which creates a secondary inflammatory response, and multiple pathophysiologic hypotheses have been proposed.<sup>108</sup> The clinical appearance is that of brawny induration, skin thickening, swelling, and tissue breakdown with ulceration in the gaiter regions. Alteration in the extracellular matrix is clear on histologic assessment, with extracellular disorganized collagen deposition in the dermal space and perivascular tissue cuffs.

Skin hypoxia occurs on the gaiter areas of limbs with severe venous disease and is significantly different from controls, oxygen tension ( $\text{tcPO}_2$ ) differing by more than 20 mm.<sup>109</sup> Although leukocyte trapping within the capillaries is probably not the sole cause, it is likely that leukocytes become activated, transmigrate into the vein walls, and mediate some of the observed tissue damage. Consistently, findings in punch biopsy specimens of ulcers suggest that leukocytes play a role in the dermal manifestations of CVI.<sup>110</sup> Leukocytes, macrophages, and mast cells have all been observed in immunohistochemical and electron microscopic examinations of affected dermal tissue.<sup>111</sup>

The dermal fibroblast may also be dysfunctional and allow perpetuation of the ulcer. Decreased motility, in part mediated by the microenvironment, plays a role in the impaired healing process of ulcer tissue.<sup>112</sup> Comparison of venous ulcer fibroblasts with control fibroblasts with stimulation with TGF- $\beta$  suggested that there are differences in collagen production.<sup>113</sup>

An unanswered question is why patients with similar degrees of reflux and hydrostatic pressures from CVI can be predisposed to venous ulcers. Data now suggests that iron metabolism and ulcer development are interrelated. Although commonly thought of as a consequence of all the other mechanisms of CVI, the iron deposition itself may cause tissue damage.<sup>114</sup> More convincingly, the risk of ulcer development among patients with class 4 to 6 CVI was sevenfold higher in those with the C282Y genotype, a mutation related to iron processing.<sup>115</sup>

## THROMBOPHLEBITIS

Thrombophlebitis, or venous wall inflammation associated with thrombosis, may be sterile or associated with a bacterial infection.<sup>116</sup> Most often it involves the superficial venous system, such as the great saphenous or cephalic vein, and occurs after placement of an intravenous catheter or other superficial trauma. Symptoms include pain, redness, swelling, and tenderness to palpation (often like a cord) present in the affected limb. A systemic febrile response is usually absent in noninfected cases, whereas bacterial thrombophlebitis may be a source of postoperative fever.

It is unclear whether there is a specific genetic predisposition to thrombophlebitis, but clinical factors and environment likely play the biggest roles. Migratory thrombophlebitis is a special case that was described by Trousseau in the 1800s and is specifically linked to patients with pancreatic cancer. Thrombophlebitis can also manifest superficially through Mondor's disease, in which the veins of the breast tissue, particularly in the upper outer quadrant, are affected.

Sterile phlebitis may occur in axial veins, varicosities, and is a well-recognized complication after venous stripping or endovenous ablation. An experimental study of sterile thrombophlebitis showed a typical sequence of early PMN attachment followed by transmigration and inflammatory changes. Approximately 25% of the time, thrombosis occurs before symptoms. The histologic pathology is an acute vasculitis with marked thickening, inflammatory cells, and fibrin deposition.<sup>117</sup> Later resolution involves fibrotic changes and recanalization of the venous segment at variable rates over weeks to months.

One study has shown that anticoagulation with fondaparinux for 45 days significantly decreased proximal venous thrombus propagation by approximately 85% in patients with a GSV thrombus  $\geq 5$  cm in length.<sup>118</sup> A recent RCT found that the direct oral anticoagulant (DOAC) rivaroxaban at 10 mg daily was noninferior to standard therapy with regards to the prevention of DVT, PE, and progression or recurrence of superficial vein thrombosis.<sup>119</sup> This trial included only patients at high risk of VTE: age >65 years, male sex, history of VTE, previous cancer and absence of varicose veins.<sup>120</sup>

The role of bacterial infection in directly promoting thrombosis has been described in various clinical settings.<sup>121</sup> The pathophysiology of infectious thrombophlebitis is similar to that of any closed-space infection, and bacterial antigens and proteins may directly stimulate venous thrombosis and the extrinsic pathway. Organisms that can be cultured from infectious thrombophlebitis include both Gram-positive and Gram-negative species.

## VENOUS ANEURYSMS

Venous aneurysms are relatively rarely encountered in the clinical setting. The most common type, isolated popliteal venous aneurysm, has an estimated incidence of only 0.1%–0.2%.<sup>122</sup> The presentation varies, from asymptomatic to CVI to PE.

Histology of affected venous segments demonstrates marked inflammatory cell infiltrate.<sup>123</sup> Elevated MMP-2 activity, also implicated in varicose vein development, is evident in aneurysmal veins as well.<sup>124,125</sup> Treatment is surgical with excellent patency results described: tangential resection with lateral veinorrhaphy excision with re-anastomosis or interposition grafting, or open or closed plication.<sup>126</sup>

## CONCLUSION

Chronic venous insufficiency is a common disease, with variable severity of symptoms, and primarily limb disability sequelae. Venous thrombogenesis and the pathophysiology of the resulting vein wall damage remains a fruitful area of study, due to limb disability and risk of death. Fortunately, the National Institutes of Health, the International Society of Thrombosis and Haemostasis, and the American Heart Association have put forth resources for investigators to study this disease. Some major gaps to be addressed include therapies to promote thrombus dissolution without bleeding risk of anticoagulation, and therapies to directly treat and reverse PTS.

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A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com).

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# Lymphatic Pathophysiology

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Dedicated to the memory of Charles L. Witte, MD (1935–2003), beloved husband and father, and great teacher, researcher, and clinician. He was the primary author of the first version of this chapter and an internationally recognized authority in the field of lymphology.

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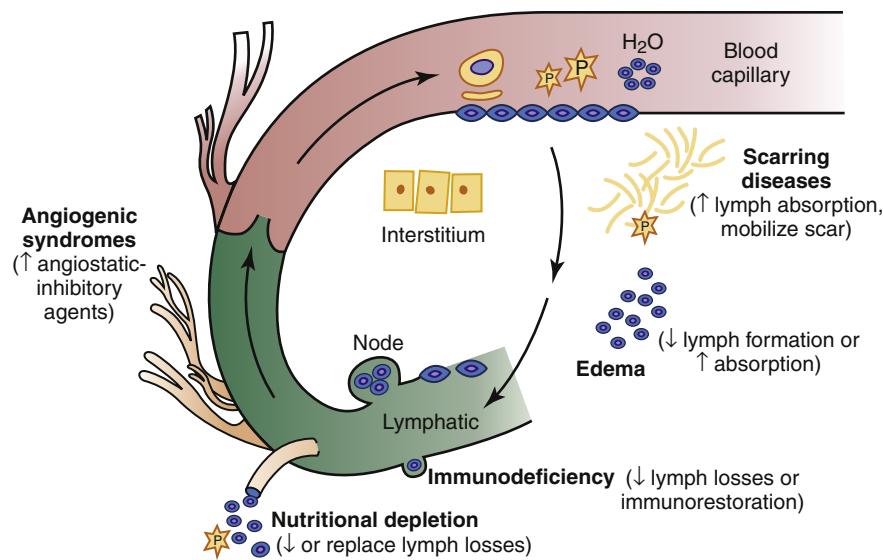
In a narrow sense, the lymph circulation is a unidirectional vascular system that merely transports surplus tissue fluid back to the bloodstream. In a broader sense, however, this network stabilizes the mobile intercellular liquid and extracellular matrix microenvironment to ensure parenchymal cellular integrity and function.

In its entirety, the lymphatic system is composed of vascular conduits: lymphoid organs, including the lymph nodes, spleen, Peyer patches, thymus, and nasopharyngeal tonsils; and cellular elements that circulate in the liquid lymph, such as lymphocytes and macrophages. These migrating cells cross the blood–capillary barrier along with a multitude of immunoglobulins, polypeptides, plasma protein complexes, and cytokines and enter the lymphatics to return to the bloodstream. Although body water circulates very rapidly as a plasma suspension of red blood cells within the blood vascular compartment,

it percolates slowly outside the bloodstream as a tissue fluid–lymph suspension of lymphocytes through lymph vessels and lymph nodes. As a specialized subcompartment of the extracellular space, therefore, the lymphatic system completes a closed loop for the circulation by returning liquid, macromolecules, and other blood elements that “escape” or “leak” from blood capillaries (Fig. 10.1).

## ANATOMY

Although, historically, identification of lymphatic vessels has long been hampered by lack of readily identifiable structures, early physicians from Hippocrates (460–377 BCE) to Aristotle (384–322 BCE) and Erasistratus (310–250 BCE) did describe vessels and nodes and on occasion visible intestinal lymphatic vessels in recently fed animals (see Kanter<sup>1</sup> for details). After



**Figure 10.1 Blood–Lymph Circulatory Loop.** Within the bloodstream, liquid flows rapidly as a plasma suspension of erythrocytes; outside the bloodstream, it flows slowly as a tissue fluid–lymph suspension of immunocytes through the lymphatics and lymph nodes. Small and large molecules, including plasma protein, trafficking cells, particulates, and respiratory gases, cross the blood–capillary endothelial barrier, percolate through the tissues, enter the lymph stream, and return to the central venous system to complete the loop. Clinical disorders of the blood–lymph circulatory loop are manifested as swelling, scarring, immunodeficiency, nutritional depletion, and uncontrolled lymphangiogenesis and angiotumorigenesis. Current and potential future therapeutic approaches are in parentheses.

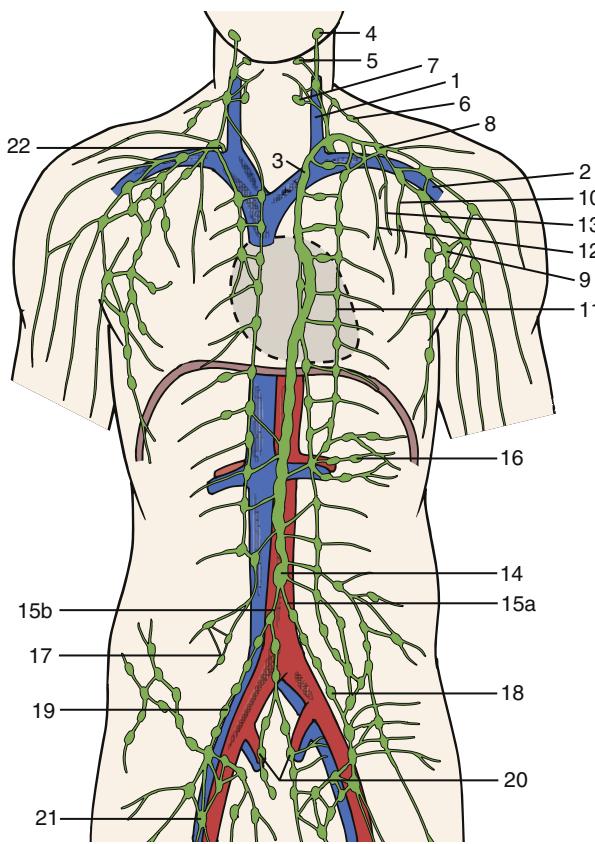
a period of little scientific advancement, discovery of chylous mesenteric lacteals in a well-fed dog by Gasparo Aselli in early in the 17th century (coincidentally the same time that Harvey described the circulation of blood) set off a flurry of anatomic dissections in England and continental Europe that established the nearly ubiquitous presence of lymphatics throughout the body and their important role in absorption of nutrients (Box 10.1).<sup>2</sup> These lymphatic “absorbents” accompany venous trunks everywhere, except in the central nervous system and cortical bony skeleton but the latter have their own special lymph drainage systems.

## Macroscopic Anatomy

In general, lymph from the lower part of the torso and viscera enters the bloodstream via the thoracic duct at the left subclavian–jugular venous junction (see Figs. 10.1 and 10.2). Lymphatics from the head and neck and from the upper extremities enter the central veins either independently or by a common supraclavicular cistern. Numerous interconnections exist within this rich vascular network, and subvariant anatomic pathways are plentiful. For example, the bulk of cardiac and pulmonary lymph empties into the great veins in the right side of the neck. In contrast, intestinal lymph, which transports cholesterol, fat-soluble vitamins, and long-chain triglycerides as chylomicra, courses retroperitoneally to the aortic hiatus and with other visceral and retroperitoneal lymphatics forms the multichannel cisterna chyli and thoracic duct. The bulk of lymph formed in the liver flows retrograde or countercurrent to portal blood and joins intestinal lymph collectors just before

### BOX 10.1 Landmarks in Lymphology

- Discovery of chyliferous vessels and “imaging” of the lymphatic system—Gaspar Aselli, 1627
- Lymph as the milieu intérieur (internal environment)—Claude Bernard, 1878
- Transcapillary exchange of liquid, lymph formation, and edema—Ernest Starling, 1895
- Embryology and phylogeny of lymphatic system—F. Sabin, O. Kampmeier, 1903
- Transcapillary protein movement and lymph absorption—A. Krogh, C. Drinker, H. Mayerson, F. C. Courtice, 1925
- Lymphangiogenesis *in vivo*, 1932, and *in vitro*, 1984
- Lymphocyte migrant streams—J. Yoffey, B. Morris, J. Gowans, 1939
- Lymphatic imaging/classification—J. Kimmonth, M. Servelle, F. Kaindl, 1950
- Intrinsic contractility and distinctive ultrastructure of lymphatics—J. Hall, I. Roddie, J. Casley-Smith, L. Leak, 1962
- Lymphostatic disorders and/or edematous states—I. Rusznyak, G. Szabo, M. E. Földi, W. Olszewski, A. Dumont, M. C. Witte, 1960
- Lymphoscintigraphy, including sentinel node mapping, 1970
- Founding National Lymphedema Network internationally linking patients/health professionals/public in lymphatic disease support/education/research/care—S. Thiadens, 1987
- Highly specific molecular and/or histochemical markers – LYVE-1, Prox-1, podoplanin, 5'-nucleotidase, VEGFR-3—1990
- Lymphatic growth factors and/or genetics—K. Alitalo, 1996, VEGFC; teams from the University of Pittsburgh and Connecticut and St George, UK (VEGFR3, Vascular endothelial growth factor receptor); Arizona/Michigan, FOXC2 1998, 2000; Leuven and Rome, present
- Magnetic Resonance Central Lymphangiographic Imaging (MRL) and Intervention (intranodal, percutaneous, endovascular)—C. Cope, later joined by M. Itkin, U Pennsylvania, 1996



**Figure 10.2** Macroscopic Anatomy of the Lymphatic System Including Major Vessels, Structures, and Nodes in Relation to Major Arteries and Veins. 1, Left internal jugular vein; 2, left subclavian vein; 3, thoracic duct; 4, parotid lymph nodes; 5, submandibular lymph nodes; 6, accessory and comitant lymph nodes of the accessory nerve; 7, internal jugular lymph nodes with left jugular trunk; 8, supraclavicular lymph nodes with left supraclavicular trunk; 9, axillary lymph nodes with left subclavian trunk; 10, intercostal lymph nodes with left intercostal trunk; 11, parasternal lymph nodes with parasternal trunk; 12, anterior mediastinal lymph nodes with left anterior mediastinal trunk; 13, tracheobronchial lymph nodes with left tracheobronchial trunk; 14, cisterna chyli; 15a, left lumbar trunk; 15b, right lumbar trunk; 16, mesenteric lymph nodes; 17, lumbar lymph nodes; 18, left common iliac lymph nodes; 19, right external iliac lymph nodes; 20, internal iliac; 21, inguinal lymph nodes; 22, right lymphatic duct. (Modified from Kubik S. In: Földi M, Földi E, eds. *Földi's Textbook of Lymphology*. 3rd ed. Munich: Urban & Fischer; 2012.)

the origin of the thoracic duct. Although these topographic variants influence development and progression of peripheral (lymph) edema only indirectly, they are nonetheless essential for a broad understanding of edema syndromes, including those accompanied by abnormal visceral lymphatics, celomic effusions, and chylous reflux.

Although the retina and brain do not technically have lymphatic apparatuses, they possess analogous circulations, such as the aqueous humor canal of Schlemm (the anterior chamber of the eye) or the cerebrospinal fluid/subarachnoid villus (pacchionian bodies) connections (the brain). The initial path postulates that the natural vasomotion of cerebral intraparenchymal arteries/arteriole generates a force that forces fluid from the perivascular space into the brain parenchyma crossing the glial perivascular sheet via water pores present in the membrane of glial cytoplasmic projections. Once in the parenchyma, the

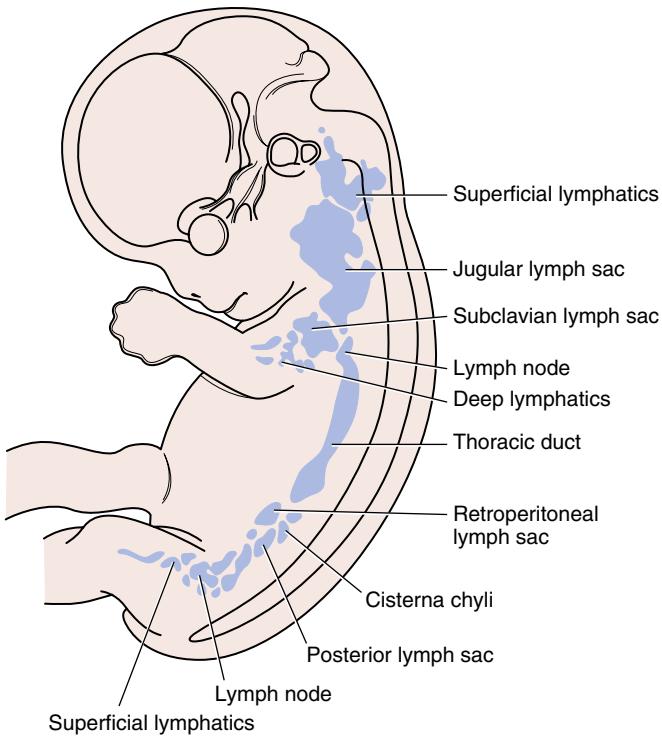
interstitial fluid travels following either a convective or diffusive trajectory<sup>3,4</sup> towards adjacent perivascular spaces (the intraparenchymal peri-arterial drainage pathway towards adjacent paravascular spaces (the intraparenchymal peri-arterial drainage pathway,<sup>5,6</sup> where it is transported to the meningeal space, thus entering the second pathway. In the meningeal space, interstitial fluid is collected into initial lymphatic capillaries present within the dura mater, which drains directly into afferent lymphatic vessels located in the cervical region, in particular into deep cervical lymphatic vessels.<sup>7,8</sup> In addition, other pathways exist within the central nervous system and eyes that drain interstitial fluid and cerebrospinal fluid including the aqueous humor. Glial elements and non-endothelial-lined intracerebral perivascular (Virchow–Robin) spaces form the glymphatic system drains the CSF, perivascular spaces and interstitial fluid of the brain swept up by astrocytic foot processes and empties into the endothelial-lined meningeal lymphatic capillaries and thence to the contractile collecting cervical lymphatics and lymph nodes.<sup>9</sup>

Extensive interruption of the cervical lymphatic trunks (e.g., after bilateral radical neck dissection) therefore causes prominent facial suffusion and a transient neurologic syndrome resembling pseudotumor cerebri,<sup>10</sup> whereas an infusion of crystalloid solution directly into the canine cisterna magna causes an elevation in intracranial pressure and increases lymph flow from draining neck lymphatics.<sup>11,12</sup> Although abundant lymphatic pathways thus exist for surplus tissue fluid to return to the bloodstream, homeostasis still depends on an unimpeded, intact, interstitial–lymph fluid circulatory system (see Figs. 10.1 and 10.2).

## Embryonic Development

Controversy has persisted since the early 1900s about the embryologic origin of lymphatics, that is, lymphovasculogenesis (endothelial precursors or stem cells, such as lymphangioblasts, differentiate and proliferate into a primitive tubular network) and subsequent lymphangiogenesis (sprouting from existing vessels; see Box 10.1).<sup>13</sup> According to Sabin, the primary lymphatic plexuses derive from central veins and their growth progresses centrifugally by sprouting toward the periphery and ultimately forming the superficial lymphatic system (Fig. 10.3).<sup>14</sup> In contrast, Kampmeier,<sup>15</sup> after a review of serial tissue sections, including Sabin's original human embryo preparations, and phylogenetic considerations, proposed the centripetal theory that the lymphatic system arises independently from tissue mesenchyme in peripheral tissues and the surrounding primary lymph sacs and only later joins the central venous system.

Recent studies of the growth regulatory gene *PROX1*<sup>16</sup> and the receptor for lymphatic vascular endothelial growth factor (VEGFR-3)<sup>17</sup> supported the centrifugal theory (origin from venous sprouting). Yet, other elegant work has demonstrated a substantial centripetal contribution from mesenchymal lymphangioblasts in the engrafted wing lymphatic system of chimeric quail chick embryos<sup>18</sup> and early avian embryos through *PROX1* staining.<sup>19</sup> Both processes may contribute in



**Figure 10.3** The developing lymphatic system showing the primary lymph sacs and the thoracic duct primordium, as well as several lymph nodes of a 2-month-old human embryo. (Modified from Sabin FR. On the origin and development of the lymphatic system from the veins and the development of the lymph hearts and the thoracic duct in the pig. *Am J Anat.* 1902;1:367, and Yoffey JM, Courtice FC. *Lymphatics, Lymph and the Lymphomeloid Complex.* New York: Academic Press; 1970.)

various degrees to the ultimate link between the lymph and blood vasculature (e.g., the cervical thoracic duct/venous junction in humans).<sup>19</sup>

### Light Microscopic Anatomy

As an efferent vascular system, the lymphatics originate within the interstitium as specialized capillaries, although in certain organs, such as the liver, they seem to emanate from nonendothelialized precapillary channels (e.g., the spaces of Disse).<sup>20</sup> Lymphatic capillaries are remarkably porous and readily permit the entry of even large macromolecules (molecular weight >1000 kD). In this respect, they resemble the uniquely “leaky” fenestrated sinusoidal blood capillaries of the liver but are in distinct contrast to most other blood capillaries, which are relatively impervious to macromolecules even the size of albumin (molecular weight, 69 kD).<sup>21</sup>

Under light microscopy without treatment, it is difficult to distinguish between blood and lymph vessels, although the latter are usually thin walled and tortuous, have a wider, more irregular lumen, and are largely devoid of red blood cells. Many staining features have been advocated to differentiate between blood and lymph microvasculature, such as the endothelial marker factor VIII-related antigen: von Willebrand factor (vWF). Although staining characteristics vary in both normal and pathologic states and at different sites (perhaps related to

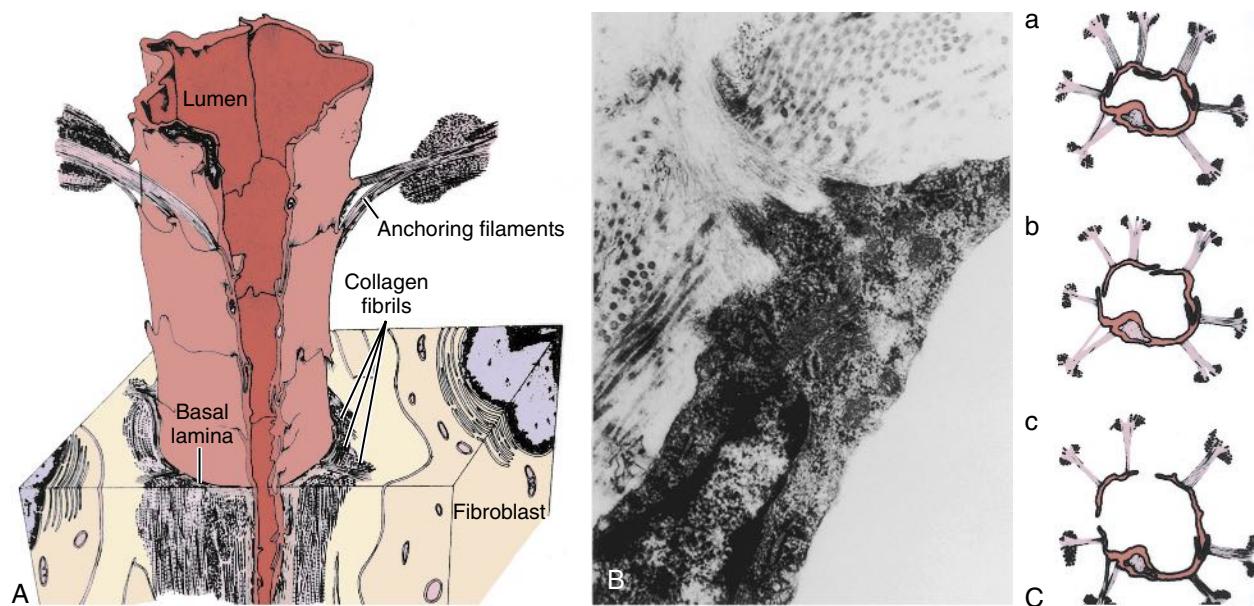
endothelial cell de-differentiation), in general, lymphatic staining resembles but is less intense than its blood vessel counterpart. In other words, the staining differences have been more quantitative than qualitative.<sup>22–29</sup>

### Lymphatic-Specific Markers

Lymphatic vessels can increasingly be distinguished from blood vessels in tissue sections by whole-mount staining with specific markers.<sup>30</sup> Only 20 years ago, little histochemical specificity existed to distinguish lymphatic vessels from blood capillaries and veins, and identification was based primarily on morphology, distinctive ultrastructure, or both. One of the most commonly used and most specific markers in use today is LYVE-1<sup>31,32</sup> with D-240 widely used to stain clinical specimens. LYVE-1 has been applied to tissues ranging from early mouse embryo to adult human and highlights initial collecting vessels and lymphatic capillaries (but not larger-caliber lymphatics). The LYVE-1 receptor appears to be a key entry point for dendritic cells to selectively access the lymphatic system.<sup>32</sup> Another strong marker localizing to the nucleus of lymphatic endothelial cells and adaptable to multiple tissues is the transcription factor PROX1.<sup>33</sup> Podoplanin recognizes a transmembrane glycoprotein<sup>34</sup> in lymphatics but not blood vessel endothelial cells in the mouse, whereas its human analogue, D2-40,<sup>35</sup> also sharply distinguishes lymphatic from blood vessel endothelium and larger collecting lymphatics which may not stain with LYVE-1 but stains other distinguishable cells. This feature has been useful in identifying preexisting and new lymphatics in tumor specimens and in generating quantitative differentials from blood vessels and indices of lymphatic invasiveness and tumor dissemination.<sup>35</sup> 5-Nucleotidase staining is used by research laboratories for its lymphatic specificity<sup>36</sup> and other common markers showing some cross-reactivity to veins include VEGFR-3<sup>15</sup> and neuropilin-2<sup>37</sup> (reviewed elsewhere).<sup>38,39</sup> Thus an array of lymphatic markers are now available to distinguish lymphatics from blood vessels, although there is overlap of cell types in normal conditions and even more so in pathologic states.

### Ultrastructure

Ultrastructurally, lymph capillaries display both “open” and “closed (tight)” endothelial junctions, often with prominent convolutions and these capillaries can dramatically adjust their shape and lumen size. Unlike blood capillaries, a basal lamina (basement membrane) is tenuous or lacking altogether in lymph capillaries.<sup>40,41</sup> Moreover, complex elastic fibrils, termed *anchoring filaments*, tether the outer portions of the endothelium to a fibrous gel matrix in the interstitium.<sup>42–44</sup> These filaments allow the lymph microvessels to open wide, which causes a sudden increase in tissue fluid load and pressure, in contrast to the simultaneous collapse of adjacent blood capillaries (Fig. 10.4). Just beyond the lymph capillaries, which have a “button” structure, are the terminal lymphatics, which have a “zipper” structure.<sup>45</sup> In contrast to more proximal and larger lymph collectors and trunks, the terminal lymphatics are



**Figure 10.4** (A) Lymphatic capillary reconstructed from collated electron micrographs. The lymphatic anchoring filaments originate from the abluminal surface of the endothelial cells and extend into adjacent collagen bundles, thereby forming a firm connection between the lymphatic capillary wall and the surrounding interstitium. (B) Transmission electron micrograph demonstrating anchoring filaments (AF) that derive from the lymphatic endothelium and join nearby collagen bundles. (C) Response of lymphatic capillaries to an increase in interstitial fluid volume. As the tissue matrix expands, tension on the AF rises, and the lymph capillaries open widely to allow more rapid entry of liquid and solute (*a* to *c*). In contrast to stretching of the lymph capillaries, a rise in matrix pressure collapses the blood capillaries, thereby restricting further plasma filtration. (From Leak LV, Burke JF. Ultrastructural studies on the lymphatic anchoring filaments. *J Cell Biol*. 1968;30:129–149; and Leak LV. Electron microscopic observation on lymphatic capillaries and the structural components of the connective tissue–lymph interface. *Microvasc Res*. 1970;2:361–391.)

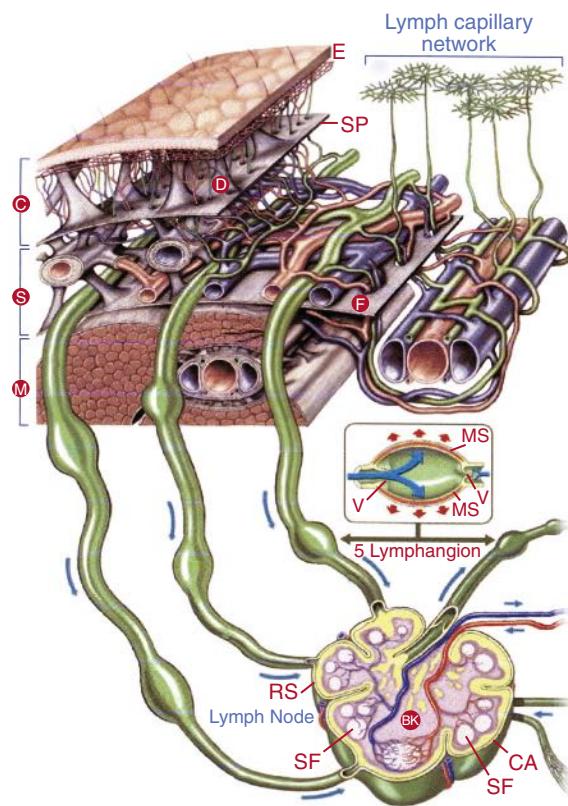
devoid of smooth muscle, although the endothelial lining is rich in the contractile protein actin.<sup>46</sup> Intraluminal bicuspid valves are also prominent features and serve to partition the lymphatic vessels into discrete contractile segments termed *lymphangions*.<sup>46</sup> These specialized microscopic features support the delicate lymphatic apparatus's functions of absorbing and transporting elements and the large protein moieties, cells, and foreign agents of the bloodstream (e.g., viruses, bacteria) that gain access to the interstitial space (Figs. 10.5 and 10.6).

### Structural–Functional Imaging

Early physicians were able to visualize the lymphatic system only by observing chyle-filled mesenteric lymphatics. Aselli's initial publication<sup>47</sup> included what has been reported as the first color anatomic plate in history.<sup>1</sup> This was followed by intralymphatic injection of mercury into cadavers by Nuck in 1692, which depicted fine channels,<sup>48</sup> then the detailed and elegant work of Mascagni in 1787,<sup>49</sup> and subsequently, the classic images of both subcutaneous and deep vessels by Sappey in 1874.<sup>50</sup> Von Recklinghausen used silver nitrate, which allowed imaging to take place without removal of surrounding tissue and facilitated visualization of lymphatic vessels as distinct from blood capillaries.<sup>51</sup> Gerota developed a technique in 1896 of injecting a mixture of Prussian blue and turpentine to highlight the vessels,<sup>52</sup> and this was followed in 1933 by the intracutaneous injection of vital dyes that bind to tissue proteins

by Hudack and McMaster,<sup>53</sup> which is a technique still used today for investigation and in the clinic (Fig. 10.7).

Modern imaging techniques also include direct (intralymphatic) injection of oily contrast agents, termed lymphangiography, first described by Kinmonth in 1954,<sup>54</sup> and whole-body lymphangioscintigraphy after subcutaneous or intradermal injection of protein-bound radiotracers<sup>55,56</sup> (see Fig. 10.7), which can provide a dynamic whole body image of the lymphatic system – peripheral and central – but with limited resolution spatially, and is useful for screening and monitoring the course of disease and effects of intervention noninvasively. SPECT-CT can greatly improve the sensitivity and localization with 3D higher resolution LAS images.<sup>57</sup> Other agents used for indirect lymphography include various fluorescent or magnetic particles,<sup>58,59</sup> infrared particles and dyes,<sup>60–63</sup> immunoglobulin conjugates,<sup>64</sup> and microbubbles<sup>64</sup> for detection with fluorescent microscopes, optical imaging systems, computed tomography (CT), magnetic resonance imaging (MRI; with and without contrast)<sup>65–73</sup> and ultrasound,<sup>74</sup> including in combination with light as photoacoustics, with an expanding potential for highly specific molecular imaging. New contrast agents and techniques continue to be developed. Most important has been the refinement of percutaneous MR imaging with direct puncture of central lymphatics and also inguinal node injection of contrast to open up the central lymphatic system to clear view and, with it, the opportunity to intervene therapeutically through gluing leaks or performing endovascular



**Figure 10.5** The lymphatic system consists of an initial superficial valveless network of endothelium-lined vessels connected to a deep valved collector system (lymphangion pumping segments defined by the valves). The deeper vessels run alongside major blood vessels and drain through lymph nodes to the main collectors; they ultimately empty into the thoracic duct or the right lymphatic duct. *BK*, blood capillary network; *C*, cutis; *CA*, capsule; *D*, dermis; *E*, epidermis; *F*, fascia; *M*, musculature; *MS*, muscle layer; *RS*, marginal sinus; *S*, subcutis; *SF*, second follicle; *SP*, subcutaneous pseudofascia; *V*, lymphatic valves. (Modified with permission from BSN-Jobst Emmerich Conception, 2002.)

stent graft shunts, with other image-guided assistance or direct surgical lymphatic venous shunts for thoracic duct decompression.<sup>66–69</sup> Photoacoustic imaging for resolution and depth improvement shows promise. ICG lymphography has been used effectively for staging of severity and operability in preparation for supermicrovascular lymphatic–venous shunt procedures to treat limb lymphedema.

## PHYSIOLOGY

*Any protein which leaves these vessels...is lost for the time to the vascular system...it must be collected by lymphatics and restored to the vascular system by way of the thoracic or right lymphatic duct.*

—Physiologist Ernest Starling, 1897

### General Principles

As a fine adjuster of the tissue microenvironment, the lymphatic system is often neglected in most treatises on vascular diseases. Yet this delicate system, so inconspicuous during life

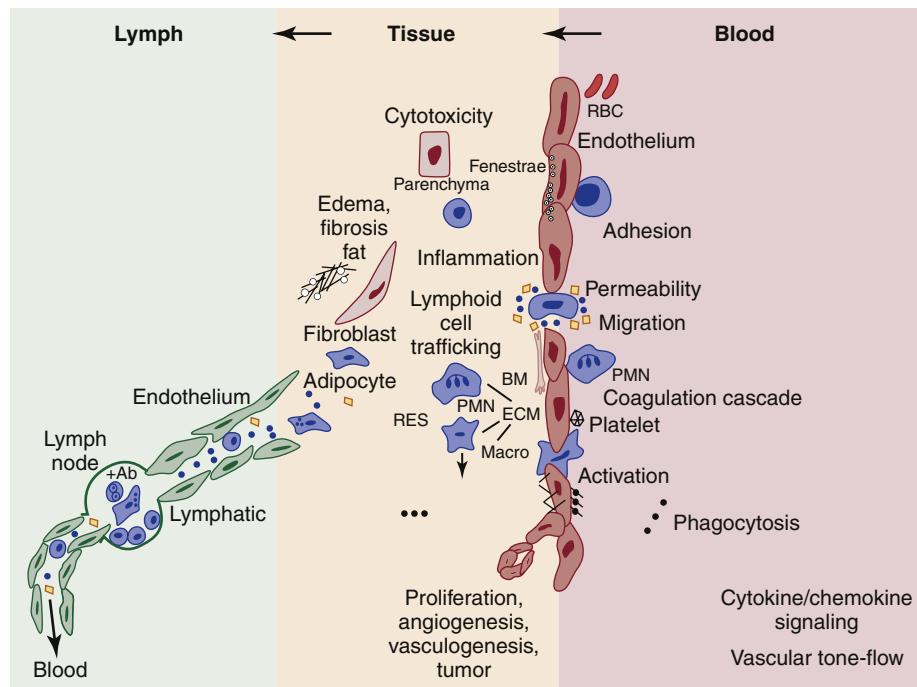
and collapsed after death, helps to maintain the liquid, protein, and osmotic equilibrium around cells and aids in absorption and distribution of nutrients, disposal of wastes, and exchange of oxygen and carbon dioxide in the local milieu intérieur.

### Interstitial (Lymph) Fluid

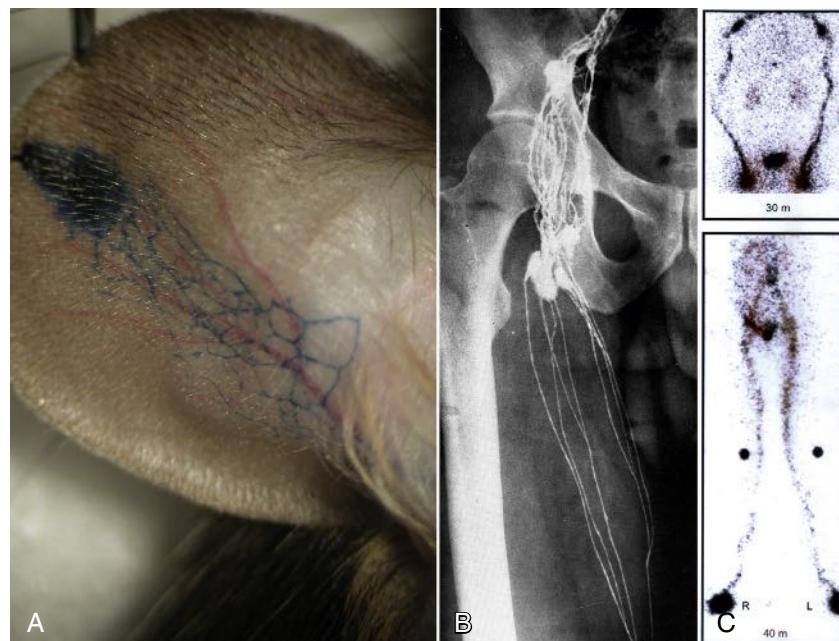
Two-thirds of the body is composed of water, and most of this liquid volume is contained within cells. However, the remainder that exists outside cells continuously circulates. In a series of epochal experiments conducted more than a century ago, the English physiologist Ernest Starling outlined the pivotal factors that regulate partitioning of the extracellular fluid.<sup>75,76</sup> In brief, the distribution of fluid between the blood vascular compartment and tissues and the net flux of plasma escaping from the bloodstream depends primarily on the transcapillary balance of hydrostatic and protein osmotic pressure gradients as modified by the character (i.e., hydraulic conductance) of the filtering microvascular surface (Fig. 10.8; also see Box 10.1). Normally, a small excess of tissue fluid forms continuously (net capillary filtration), and this surplus enters the lymphatic system and returns to the venous system. In contrast to blood, which flows in a circular pattern at several liters per minute, lymph flows entirely in one direction and at rest at a rate of only 1.5 to 2.5 L/24 hour. This limited volume derives from a slight hydrodynamic imbalance that favors movement of fluid, salt, and macromolecules from plasma into tissue spaces. Although blood capillary beds vary in hydraulic conductance, in general, disturbances in the transcapillary hydrostatic and protein osmotic pressure gradients (Starling forces) tend to promote edema that is low in protein content (<1.0 g/dL [10 g/L]), whereas impedance to lymph flow (lymph stasis) promotes (lymph) edema that is high in protein content (>1.5 g/dL [15 g/L]).

Unlike blood flow, which is propelled by a powerful and highly specialized muscular pump (the heart), propulsion of lymph originates predominantly from spontaneous intrinsic segmental contractions of larger and probably also small lymph trunks,<sup>77–79</sup> and to less extent, from extrinsic “haphazard forces” such as breathing, sighing, yawning, muscular squeezing (e.g., alimentary peristalsis), and transmitted arterial pulsations (Table 10.1).<sup>79,80</sup> As noted, the contractions of lymphatic segments between intraluminal valves (i.e., the lymphangions) are highly responsive to lymph volume. Thus, an increase in lymph formation is accompanied by more frequent and more powerful lymphangion contractions, a lymphodynamic response that resembles Starling’s other major physiologic principle, the law of the heart.<sup>46,81</sup>

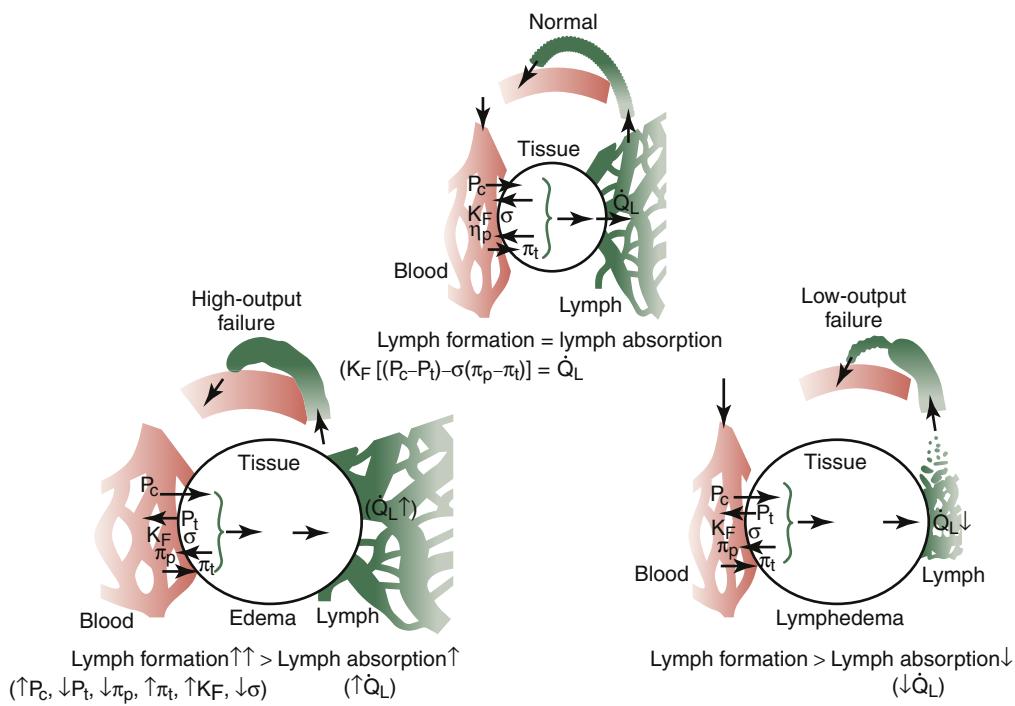
Lymphatic truncal contraction, like venous and arterial vasomotion, is mediated by sympathomimetic agents (both  $\alpha$ - and  $\beta$ -adrenergic agonists),<sup>82,83</sup> byproducts of arachidonic acid metabolism (thromboxanes and prostaglandins),<sup>84–87</sup> and neurogenic, even pacemaker stimuli<sup>88,89</sup> and by factors produced by lymphatic endothelium. Oddly, in different regions of the body, lymphatic trunks exhibit varying sensitivity to different vasoactive and neurogenic stimulants.<sup>90,91</sup> Although the importance of truncal vasomotion as mediated by tunica smooth muscle is well established, it remains unclear whether terminal lymphatics or capillaries are also capable of vasomotion or are simply passive channels.



**Figure 10.6** The postulated role of endothelial processes in microcirculatory events that have a bearing on angiogenesis in the blood–lymph loop. Such processes include macromolecular and liquid permeability, vasoresponsiveness, leukocyte adhesion and transmigration, coagulation cascading, particulate phagocytosis, antigen presentation and cytokine activation, lymphoid cell trafficking, and proliferative events leading to new vessel or tumor growth. Many mediators of these events have been identified by studying processes implicated at the blood–vascular endothelial surface, which are likely to also occur at the lymphatic–endothelial interface. The relative anatomic and dynamic relationships between blood and lymph vascular endothelium, parenchymal and extravascular connective tissue, and transmigrating leukocytes are shown. Black circles, exogenous particulates; black square, macromolecules; open circles, fluid (plasma, interstitial, or lymph). Ab, antibody; BM, basement membrane; ECM, extracellular matrix; macro, macrophage; PMN, polymorphonuclear neutrophil; RBC, red blood cell; RES, reticuloendothelial system. (Modified from Witte MH, Dellinger MT, Papendieck CM, Boccardo F. Overlapping biomarkers, pathways, processes and syndromes in lymphatic development, growth, and neoplasia. *Clin Exp Metastasis*. 2012;29:707–727.)



**Figure 10.7** Imaging Techniques to Delineate the Structure and Function of the Lymphatic System. (A) Evans blue dye injected intradermally in the tip of a mouse ear rapidly displays the draining lymphatic channels. A similar vital dye (lymphazurin blue or isosulfan blue) is used in the clinic. (B) Classic lymphography image from Kinmonth clearly depicting the fine lymphatic vessels of the upper part of the thigh in an adult human.<sup>54</sup> (C) Radioisotope lymphangiography displaying normal lymphatic tracer transport in the arms (upper panel) and the legs (lower panel). A single injection into each hand or foot is seen at the bottom of each image, with markers at the knees in the lower panel. (Modified from Witte CL, Witte MH, Unger EC. Advances in imaging of lymph flow disorders. *Radiographics*. 2000;20:1697–1719.)



**Figure 10.8** Primary forces regulating fluid flux into the interstitium and the importance of lymph flow in maintaining steady-state interstitial fluid volume, and hence, stable partitioning of extracellular fluid between the bloodstream and the interstitium (Starling's equilibrium). Edema may occur as a result of high-output failure of lymph circulation (lymph overload with increased lymph flow) (*lower left*) or, less commonly, low-output failure (lymphedema) caused by interruption in lymph transport capacity (*lower right*).

**TABLE 10.1** Circulatory Dynamics of Vascular Conduits

	Lymphatic	Vein	Artery
Primary propulsive unit	Lymphangion	Heart	Heart
Secondary propulsive force	Haphazard <sup>a</sup>	Skeletal muscle	Vasomotion
Distal (upright) pressure (mm Hg)	2–3	90–100	20
Central pressure (mm Hg)	6–10	0–2	100
Flow rate	Very low	High	High
Vascular resistance	Relatively high	Very low	High
Intraluminal valves	Innumerable	Several	None
Impediment to flow	Lymph nodes	None	None
Conduit fluid column	Incomplete	Complete	Complete
Conduit failure	Edema (>1.5 g/dL) with brawny induration and acanthosis	Edema (<1.0 g/dL) with skin pigmentation and “stasis” ulceration	Claudication, rest pain, tissue necrosis

<sup>a</sup>Breathing, sighing, yawning, peristalsis, and transmitted arterial pulsation; skeletal muscle contraction also increases the amplitude and frequency of lymphatic contractions and squeezes interstitial fluid into the initial lymphatics (i.e., lymph capillaries).

### Lymph Nodes

In addition to their central immunologic role, lymph nodes are a potential site of impediment to the free flow of lymph. Unlike frogs, which lack lymph nodes but possess four or more strategically placed lymph hearts that propel large quantities of peripheral lymph back to the bloodstream,<sup>92,93</sup> mammals possess immunoreactive lymph nodes, which, when swollen, fibrotic, or atrophic, may act to initiate or perpetuate lymph stasis.<sup>78,79</sup>

### Flow–Pressure Dynamics

Although lymphatic vessels, like veins, are thin-walled flexible conduits that return liquid to the heart, the flow–pressure relationships in the venous system and the lymphatic system are different. The energy to drive blood in the venous system derives primarily from the thrust of the heart. The cardiac propulsive boost maintains a pressure head through the arteries and blood capillaries into the veins. In contrast, lymph vessels in tissues

are not directly contiguous with the blood vasculature, and the chief source of energy for propulsion of lymph emanates from the intrinsic lymphatic trunkal wall contractions (propulsor lymphaticum).<sup>77–93,96,97</sup> Like amphibian lymph hearts (cor lymphaticum), mammalian lymphatic smooth muscle beats rhythmically and in a coordinated fashion. Contractile waves propagate rapidly from one edge of the lymphatic trunk to the other, in the direction of tissue-to-lymph node (afferent lymphatic vessels) or lymph node-to-venous system (efferent lymphatic vessels). Contractile waves coupled to a the presence of a well-developed intraluminal valve system, facilitates transport of lymph.<sup>98</sup> In a sense, the lymphatic structures function as micropumps that respond to fluid challenges, and small rises in intraluminal pressure can lead to dramatic increases in contractile frequency, for example, in popliteal afferent lymphatic vessels, raising the intraluminal pressure 1 mm Hg triples contractile frequency purportedly improving movement of lymph.<sup>99</sup> Ordinarily, resistance to flow in the lymphatic vessels is relatively high in comparison to the low resistance in the venous system,<sup>100</sup> but the pumping capacity of the lymphatics is able to overcome this impedance by generating intraluminal pressures of 30 to 50 mm Hg and sometimes even equaling or exceeding arterial pressure.<sup>77,100,101</sup> This formidable lymphatic ejection force is modulated not only by filling pressure but also by temperature, sympathomimetics, neurogenic stimuli, circulating hormones, and locally released paracrine and autocrine cytokine secretions.<sup>102</sup>

The pacemaking activity present in lymphatic vessels is responsible for coordinating contractions and setting their rhythm, consequently affecting lymph flow. Lymphatic contractions are a result of action potentials that originate within the lymphangion, likely due to activity of pressure-sensitive chloride ion channels in lymphatic smooth muscle cells.<sup>103</sup>

Another recent advance in the understanding of the pacemaking activity is its point of origin. Theoretically, any smooth muscle cell in the wall of lymphatic vessels can act as a pacemaker, and the rhythm is set by the cell that is faster in firing an action potential, which propagates through the lymphangion wall. An *in silico* analysis of experimental data suggests that the most likely sites of pacemaker activity are adjacent to the intraluminal valves. At these sites, cell density and cell-to-cell communication seem to be ideal to generate action potentials that propagate through the connected muscular layer leading to an organized contraction.<sup>104</sup>

It is often mistakenly thought that lymph return, like venous return, is directly enhanced by truncal compression from skeletal muscle and other adjacent structures. Although muscular contraction and external massage clearly accelerate lymph return in the presence of edema,<sup>105</sup> under normal conditions, peripheral lymph flow is regulated primarily by spontaneous contraction of the lymphatics themselves.<sup>101,102</sup> In peripheral lymphatics, unlike peripheral veins, the column of liquid is incomplete. Accordingly, with normal intralymphatic pressure, external compression is ineffective in propelling lymph onward, although it may increase the frequency and amplitude of lymphatic contractions. In other words, lymphatics, in contrast to veins, are not sufficiently “primed.”<sup>105</sup> During

lymphatic obstruction and persistent lymph stasis, the fluid column in the lymphatics becomes continuous, and skeletal muscle or forceful external compression then becomes an effective pumping mechanism that aids lymph transport.<sup>101,105</sup>

Studies of the effect of gravity on peripheral lymphatic and venous pressure confirm these findings. Although assuming an erect position sharply raises distal venous pressure, peripheral intralymphatic pressure is unaffected, although lymphatic truncal pulsation increases in both frequency and amplitude.<sup>105</sup> This arrangement favors removal of tissue fluid by the lymphatics during dependency because, unlike veins, the lymphatics operate at much lower hydrostatic pressure. After the lymphatics become obstructed, truncal contractions quicken at first, but then the intraluminal valves gradually give way, and as the lymph fluid column becomes continuous, this mechanical advantage is lost, and chronic lymphedema supervenes.

## Lymphatic Transport Route

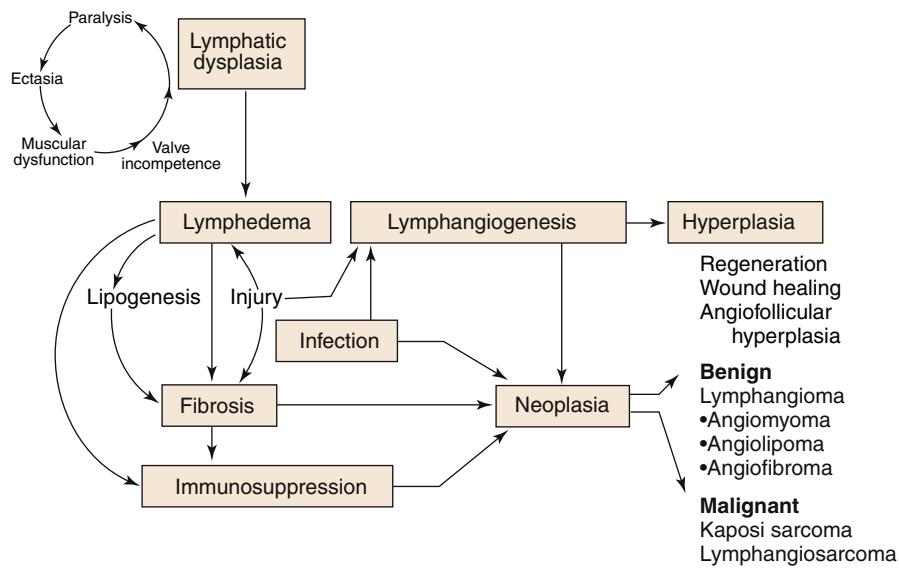
The lymphatic route of transport of liquid, protein, and macromolecules, particularly chylomicra originating in the small intestine, is well recognized, albeit underappreciated, and the lymphogenous route of cancer spread forms the conceptual basis for most current treatment approaches to solid organ cancers. The role of lymphatic uptake and clearance of microorganisms in the clinical manifestations (e.g., lymphangiitic streaking), pathogenesis, inflammatory and other tissue responses, and immune defense has been underemphasized, particularly in recent years. From the 1930s to the 1960s (see Box 10.1), a number of carefully performed studies examined the critical lymphatic route in the initial and later phases of viral and bacterial infection and the dynamic physiology of the afferent and efferent arms of the immune response.<sup>106</sup> The lymphologist Joseph Yoffey laid the groundwork for recognition of the importance of the “inert” lymphocyte and the discovery of lymphoid cell trafficking, which are fundamental to the principles of modern immunology.<sup>107–109</sup> Recasting these older investigations with more modern physiologic techniques and molecular tools may yield new translational insight into disorders ranging from AIDS and tuberculosis to parasitic disorders while also elucidating the lymphatic spread of cancer (Fig. 10.9).<sup>110–113</sup> It is likely that COVID-19 will also turn out to be an important but unrecognized lymph-borne infection.<sup>113</sup>

## MOLECULAR LYMPHOLOGY

Advances in molecular biology and the development of new techniques from the Human Genome Project have ushered in the era of molecular lymphology.

### Lymphangiogenesis

In contrast to uncontrolled new growth (lymphangiosarcoma), programmed proliferation of lymphatic endothelium with tube formation (lymphangiogenesis) is critical to a host of physiologic and pathologic processes. During the past several decades, since the phenomenon of angiogenesis was first reproduced in



**Figure 10.9** The Pathogenesis of Peripheral Lymphedema and Some of its Sequelae. According to this scheme, congenitally deficient or obstructed lymphatics promote lymph stasis, which is accompanied by deranged truncal contractility, progressive valve incompetence, destruction of contractile elements (lymphangiolysis), and gradual ectasia of lymphatic collectors. After a variable period (occult lymphedema), sometimes aggravated by environmental trauma, a series of events is set into motion that culminates in chronic lymphedema. This clinical state is characterized not only by progressive swelling but also by fat and scar deposition, immunodysregulation, a propensity for cellulitis, and microvascular proliferation; these processes are essential for repair and regeneration but may result in bizarre and poorly understood new vascular growths.

endothelial cell and mixed vascular tissue cultures,<sup>114,115</sup> considerable attention has been directed toward furthering understanding of this process, but largely in the context of blood vessel growth (hemangiogenesis).<sup>116,117</sup> The lymphatic counterpart (i.e., lymphangiogenesis) has received scant attention until recently, although lymphatic (re)generation is essential to health, and disorders of lymph flow and lymphatic growth are common, often disfiguring, and sometimes life- and limb-threatening.<sup>116</sup>

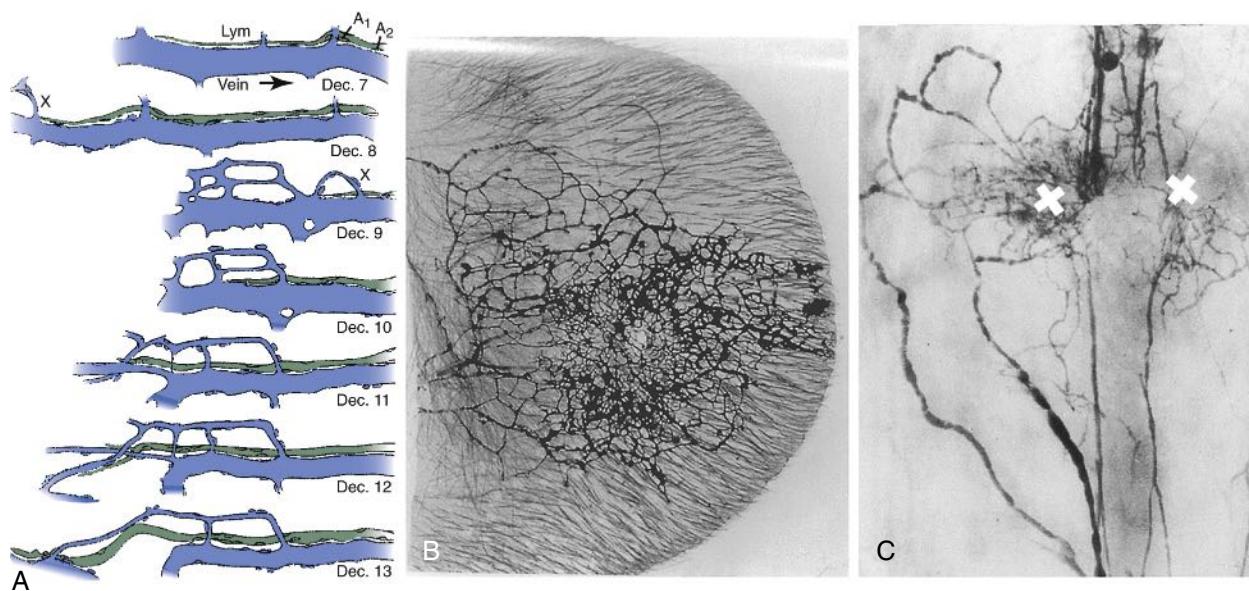
In now classic studies, Clark and Clark documented the extension of lymphatic capillaries by outgrowth from preexisting lymph vessels in rabbit ear transparent chambers (Fig. 10.10A).<sup>118,119</sup> Later, Pullinger and Florey emphasized that despite the similar appearance of each vascular endothelium, lymphatics are consistently connected to lymphatics, veins to veins, and arteries to arteries without intermingling (see Fig. 10.10B).<sup>119</sup>

After experimental hind limb circumferential skin incision, new lymphatics traverse the integumentary gap by postoperative day 4. By the eighth day, lymphatic continuity is restored anatomically (delineated by distribution of intradermal India ink particles) and physiologically (remission of transient peripheral edema).<sup>120,121</sup> Bellman and Odén meticulously documented, by Thorotrast microlymphangiography, the time course and extent of newly formed lymphatics in circumferential wounds in the rabbit ear, including lymphatic bridging through newly formed scar (see Fig. 10.10C).<sup>122,123</sup> As lymphatics increased in caliber, intraluminal valves and sinuous dilatations appeared. Subsequent studies documented

restoration of distinctive ultrastructural features in newly regenerated lymphatic vessels, including characteristic overlapping junctions and Weibel–Palade bodies (storage depots for vWF [factor VIII-related antigen]).<sup>124–127</sup>

Like the more than 1 trillion blood vascular endothelial cells that are normally dormant,<sup>127,128</sup> lymphatic endothelial cell turnover is also minuscule.<sup>129</sup> However, with injury, incorporation of tritiated thymidine into proliferating lymphatic endothelium sharply increases.<sup>129</sup> Moreover, fetal lymphatics show greater labeling than do neonatal and adult lymphatics, whereas visceral lymphatic endothelium proliferates more rapidly than does peripheral lymphatic endothelium.<sup>130</sup>

Lymphatic endothelium was first isolated *in vitro* from bovine mesenteric lymphatics<sup>24</sup> and in the same year, from a patient with a large cervicomedastinal hygroma,<sup>131</sup> and subsequently, from another patient with a retroperitoneal lymphangioma,<sup>22</sup> as well as from canine and human thoracic ducts.<sup>23</sup> Lymphatic endothelial cells from sheep, dog, mouse, rat, and ferret lymphatic collectors have now been isolated, passed in culture, and studied by techniques similar to those used for blood large-vessel and microvessel isolation. Putative lymphatic endothelium has also been isolated from mixed microvascular cultures of human foreskin and skin by separation with magnetic beads and labeling with lymphatic markers such as LYVE-1.<sup>132</sup> Lymphangiogenesis *in vitro* was first demonstrated more than 2 decades ago with the formation of tubes and cyst-like structures spontaneously<sup>131</sup> or after the addition of collagen matrix to tissue culture.<sup>133</sup>



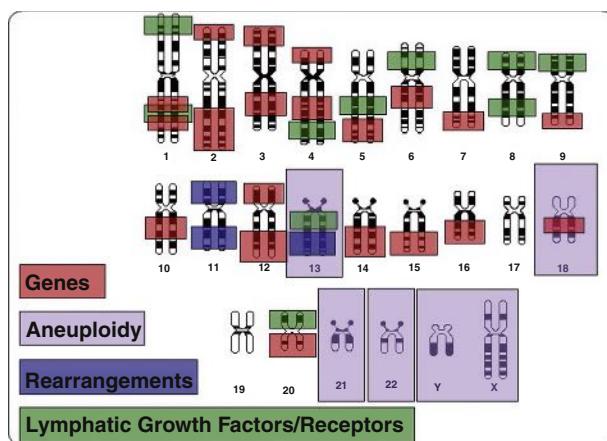
**Figure 10.10** Classic Observations on Lymphangiogenesis *in Vivo*. (A) Series of camera lucida, oil immersion records showing growth of an individual lymphatic capillary in the rabbit ear (Lym). Corresponding parts of a lymphatic and vein have been placed below one another in drawings of December (Dec) 7, 8, and 9 to 13. The drawings of Dec 9 to 13 have been moved to the right so that X represents the same spot on Dec 8 and 9. During growth of the lymphatic, there has been conspicuous retraction and disappearance of branches and loops of the blood vessel. Retraction of a short lymphatic tip is seen between Dec 11 and 13. Lymphatic endothelial nuclei are stippled. A<sub>1</sub> and A<sub>2</sub> are two daughter nuclei after a mitotic division (x177; magnification of original drawing, x700). (B) Twenty-one days after making a turpentine abscess that perforated a mouse's ear, a dense new network of lymphatic capillaries surrounds the hole (x8). (C) *In vivo* microlymphangiogram 24 days after a short transverse incision in the skin of a rabbit ear. The extent of the incision is depicted by the crosses. The distal part of the ear is uppermost. Several arcading vessels around the incision and numerous fine connections through the scar are seen. (A, From Clark ER, Clark EL. Observations on the new growth of lymphatic vessels as seen in transparent chambers introduced into the rabbit's ear. *Am J Anat*. 1932;51:49–87. B, From Pullinger DB, Florey WH. Proliferation of lymphatics in inflammation. *J Pathol Bacteriol*. 1937;45:157–170. C, From Bellman S, Oden B. Regeneration of surgically divided lymph vessels: an experimental study on the rabbit's ear. *Acta Chir Scand*. 1959;116:99–117.)

## Lymphovascular Genomics and Genotype–Phenotype Correlations

Growing evidence has confirmed that lymphangiogenesis is under genetic control (Fig. 10.11 and Table 10.2) (also see recent reviews). For example, a gene or genes expressed from non-activated portions of the inactivated X chromosome or from the Y chromosome are probably involved in lymphatic development, and a deficiency in this gene or its product(s) is responsible for Turner syndrome (XO ovarian dysgenesis), which exhibits a variety of lymphatic and other cardiovascular anomalies. Other chromosomal aneuploidies, such as trisomy 21 (Down syndrome), and rearrangements (additions, deletions, translocations) also occasionally manifest as strangulating fetal cystic hygroma, lymphedema, and intestinal lymphangiectasia and are commonly associated with early fetal demise (see Fig. 10.11).<sup>134</sup>

Both forward and reverse genetic techniques have provided clues to sites of “lymphangiogenesis genes,” and a spectrum of developmental and other hereditary lymphedema–angiodysplasia syndromes (often with autosomal dominant inheritance) have been catalogued (see Fig. 10.11).<sup>13,19,135–140</sup> They include mutations in a subpopulation of patients with Milroy syndrome

(VEGFR-3),<sup>141</sup> mutations in the transcription factor SOX18<sup>142</sup> in two families with autosomal recessive and dominant forms of hypotrichosis–lymphedema–telangiectasia syndrome, and mutations in the transcription factor FOXC2<sup>143</sup> uniformly in hundreds of patients with lymphedema–distichiasis (LD) syndrome. Interestingly, the genetically engineered haploinsufficient ( $\pm$ ) Foxc2 mouse<sup>144</sup> exhibits a double row of eyelashes and a hyperplastic lymphatic phenotype like human LD. More recently, additional mutations have been identified, including inherited generalized lymphatic dysplasia (Hennekam syndrome; CCBE1),<sup>145</sup> lymphedema type 1C (GJC2),<sup>146</sup> lymphedema–choanal atresia (PTPN14),<sup>147</sup> Emberger syndrome (GATA2),<sup>148</sup> microcephaly–lymphedema–chorioretinopathy (KIF11), Milroy-like lymphedema (VEGF-C), and oculodentodigital lymphedema (GJA1) (see review).<sup>132</sup> Other genes (HGF (OMIM1142409) and MET)<sup>149</sup> have been associated with inherited lymphedema; however, no syndrome has been linked with these genes. Additional lymphedema-associated genes recently described include CSLER-1<sup>150</sup> (OMIM604523), SEMAPHORIN3A (SEMA3A) (OMIM603961),<sup>151</sup> ADAMTS3 (OMIM605011), EPHB4 (OMIM600011), FATA4 (OMIM612411), KIF11 (OMIM148760), and ANGIOPOIETIN-2 (ANG-2).<sup>152</sup> These known mutations pinpoint just a small portion of the more than



**Figure 10.11** Genomics-proteomics of lymphedema-angiodyplasia syndromes displaying mutations of known genes (pink boxes) for a familial Milroy lymphedema subpopulation (VEGFR3 at chromosome 5q34-35), lymphedema-distichiasis (FOXC2 at chromosome 16q24), hypotrichosis, lymphedema, and telangiectasia (SOX18 at chromosome 20q13), generalized lymphatic dysplasia (Hennekam syndrome) (CCBE1 at 18q21), inherited lymphedema type 1C (GJC2 at 1q41), lymphedema–choanal atresia (PTPN14 at 1q32), and Emberger syndrome (GATA2 at 3q21) as well as linkage locations for Aagenes syndrome (chromosome 15) and Noonan syndrome (chromosome 12). In addition, aneuploidies (purple boxes) and rearrangements (blue boxes) involving other chromosomes are associated with additional lymphedema-angiodyplasia syndromes. Examples include trisomy 13, 18, 21, and 22; Klinefelter XXY; Turner XO; and chromosomal abnormalities of addition 11p and deletions 11q and 13q, all associated with lymphedema-angiodyplasia syndromes. Locations of lymphatic-specific growth and/or modification proteins and receptors (green boxes) involved in development of the lymphatic system are also displayed. (Modified from Northup KA, Witte MH, Witte CL. Syndromic classification of hereditary lymphedema. *Lymphology*. 2003;36:162–189.)

**TABLE 10.2**
**Mouse Lymphedema–Angiodyplasia Syndromes from Abnormalities and/or Altered Levels of Specific Proteins and/or Chromosomes**

	Molecular Description	Lymphatic Phenotype
<b>Extracellular Proteins</b>		
Angiopoietin-2	Ligand for the receptor tyrosine kinase Tie-2	<i>Ang2</i> <sup>-/-</sup> mice exhibit chylous ascites, lymphedema, and lymphatic hypoplasia. The mesenteric collecting lymphatic vessels of <i>Ang2</i> <sup>-/-</sup> mice lack complete coverage with smooth muscle cells, and the lymphatic capillaries in the digestive organs are associated with pericytes. <i>Ang-1</i> can correct these mutant phenotypes (Gale et al., 2002 <sup>168</sup> ; Shimoda et al., 2007 <sup>210</sup> )
Fasting-induced adipose factor	Glycosylated secreted protein	<i>Fiaf</i> <sup>-/-</sup> mice have dilated, blood-filled lymphatics in the small intestine. This phenotype begins postnatally and is not observed in <i>fiaf</i> <sup>-/-</sup> embryos (Bäckhed et al., 2007 <sup>211</sup> )
VEGF-C	Ligand for VEGFR-2 and VEGFR-3	<i>Vegfc</i> <sup>-/-</sup> mice lack jugular lymph sacs. <i>Vegfc</i> <sup>+/-</sup> mice have chylous ascites, lymphedema, and lymphatic hypoplasia (Karkkainen et al., 2004 <sup>212</sup> )
VEGF-D	Ligand for VEGFR-3	<i>Vegfd</i> <sup>-/-</sup> mice do not exhibit a striking lymphatic phenotype (Baldwin et al., 2005 <sup>213</sup> )
TgVEGF-C156S	Overexpression of the VEGFR-3-specific form of VEGF-C in the skin of mice using the keratin-14 promoter	Transgene-induced hyperplasia of lymphatic vessels (Veikkola et al., 2001 <sup>214</sup> )
TgVEGF-D	Overexpression of VEGF-D in the skin of mice using the keratin-14 promoter	Transgene-induced hyperplasia of lymphatic vessels (Veikkola et al., 2001 <sup>214</sup> )
<b>Membrane and Intracellular Proteins</b>		
Ephrin B2	Transmembrane ligand for the Eph receptor	<i>EphrinB2</i> <sup>ΔV/ΔV</sup> mice develop chylothorax and fail to undergo proper postnatal lymphatic remodeling (Mäkinen et al., 2005 <sup>215</sup> )
α <sub>9</sub> β <sub>1</sub> Integrin	Receptor for extracellular matrix	<i>19</i> <sup>-/-</sup> mice develop chylothorax (Huang et al., 2000 <sup>216</sup> )
LYVE-1	Lymphatic hyaluronan receptor	The lymphatic system develops normally in <i>Lyve1</i> <sup>-/-</sup> mice (Gale et al., 2007 <sup>217</sup> )

**TABLE 10.2**

Mouse Lymphedema–Angiodysplasia Syndromes from Abnormalities and/or Altered Levels of Specific Proteins and/or Chromosomes—cont'd

	Molecular Description	Lymphatic Phenotype
Neuropilin-2	Receptor for semaphorins and VEGF family members	<i>Nrp2</i> <sup>-/-</sup> mice have a reduction in lymphatic capillaries during development (Yuan et al., 2002 <sup>27</sup> )
Podoplanin	Membrane glycoprotein	<i>Podoplanin</i> <sup>-/-</sup> mice have lymphedema, defects in lymphatic patterning, and dilated lymphatic vessels (Schacht et al., 2003 <sup>218</sup> )
SLP-76 and Syk	Adaptor protein and tyrosine kinase, respectively	Proposed that lymphatic and blood vessels in SLP-76 and Syk mutant mice fail to separate (Abtahian et al., 2003 <sup>219</sup> ; Sezda et al., 2006 <sup>220</sup> )
Spred1/2	Signaling proteins that negatively regulate ERK activation	<i>Spred1/2</i> double-knockout embryos die because of severe hemorrhage and edema. The lymphatic vessels of <i>Spred1/2</i> double-knockout mice appear dilated and contain blood (Taniguchi et al., 2007 <sup>221</sup> )
VEGFR-3	Receptor tyrosine kinase for VEGF-C and VEGF-D	<i>Chy</i> mice have chylous ascites, lymphedema, and hypoplasia of cutaneous lymphatic vessels (Karkkainen et al., 2001 <sup>222</sup> )
Connexin 37 and Connexin 43	Gap junction proteins	Connexin 37 and 43 deficiencies in mice disrupt lymphatic valve development and result in lymphedema and chylothorax (Kanady et al., 2011 <sup>223</sup> )
PI3K	Regulatory subunit of PI3-kinases	Organ-specific (gut) lymphangiectasia, arrested lymphatic sprouting, and maturation defects (Mouta-Bellum et al., 2009 <sup>224</sup> )
Tie1 receptor	Receptor for Tie1	Loss of Tie1 receptor impairs lymphatic vessel development, resulting in developmental edema (D'Amico et al., 2010 <sup>225</sup> )
<b>Nuclear Proteins</b>		
Foxc2	Transcription factor	<i>Foxc2</i> <sup>+/-</sup> mice exhibit lymphatic reflux, extralymphatic vessels and lymph nodes, and distichiasis (Kriederman et al., 2003 <sup>144</sup> ). <i>Foxc2</i> <sup>-/-</sup> mice show defective lymphatic valves and abnormal mural cell coverage of lymphatic vessels (Petrova et al., 2004 <sup>226</sup> )
Net	Transcription factor. Net <sup>δ/δ</sup> mice lack a specific DNA-binding domain	<i>Net</i> <sup>δ/δ</sup> mice develop chylothorax and have dilated lymphatic vessels (Ayadi et al., 2001 <sup>227</sup> )
Prox1	Transcription factor	<i>Prox1</i> <sup>-/-</sup> mice fail to develop lymphatic vessels (Wigle and Oliver, 1999 <sup>16</sup> ). <i>Prox1</i> <sup>-/-</sup> mice exhibit lymphedema, chylous ascites, mispatterned lymphatic vessels, and generalized obesity (Harvey et al., 2005 <sup>177</sup> )
Sox18	Transcription factor	<i>Sox18</i> <sup>-/-</sup> mice manifest chylous ascites, depending on the genetic background (Pennisi et al., 2000 <sup>228</sup> )
Vezf1	Zinc finger transcription factor	Lymphatic hyperplasia is observed in the jugular region of E13.5 <i>Vezf1</i> <sup>+/+</sup> embryos. Lymphatic abnormalities were not observed at later time points (Kuhnert et al., 2005 <sup>229</sup> )
Tbx1	Transcription factor	Lymphatic hyperplasia and chylous ascites. Regulates Vegfr3 (Chen et al., 2010 <sup>230</sup> )
<b>Chromosomal Abnormalities</b>		
Chy3	Large deletion of chromosome 8. The gene for VEGF-C is located within this deleted region	<i>Chy3</i> mice show chylous ascites, lymphedema, and lymphatic hypoplasia (Cattanach et al., 1993 <sup>231</sup> ; Dellinger et al., 2007 <sup>154</sup> )
Ts16	Trisomy 16	Nuchal edema and distended jugular lymph sacs (Gittenberger-De Groot et al., 2004 <sup>232</sup> )

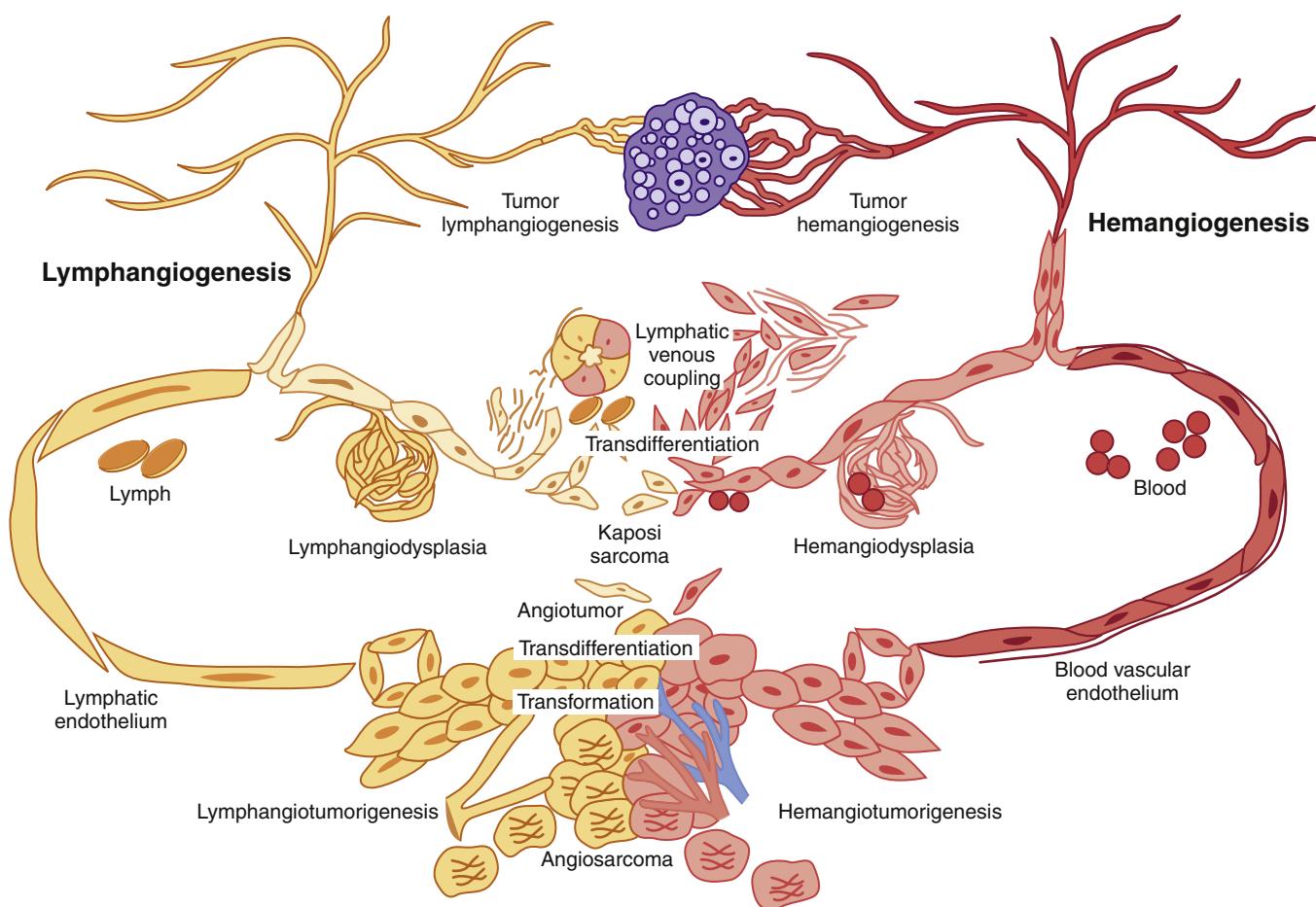
ERK, extracellular signal-related kinase; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

45 distinct Online Mendelian Inheritance in Man (OMIM) and non-OMIM familial disorders affecting the lymphatic segment of the “vasculature,”<sup>153</sup> suggesting that genes involved in normal and pathologic lymphatic growth and development span nearly the entire genome (see Fig. 10.11).

### Growth/Inhibitory Factors

Although the underlying mechanisms governing lymphangiogenesis are only beginning to be understood, a variety of stimulatory (e.g., VEGF-C and VEGF-D) and inhibitory

factors, including the angiopoietin-1–angiopoietin-2 yin-yang interaction, modulate growth, development, and remodeling of the lymphatic vasculature (see Table 10.2),<sup>138,139,154,155</sup> and others modulate vascular development, with dysfunction/function of the lymphatic vasculature in common with or distinct from the blood vasculature.<sup>13,19</sup> Insights have been gained from the invaluable transgenic, spontaneous, and chemical-and/or radiation-induced mutant mouse models (see Table 10.2). These angiomodulatory factors should be crucial to understanding clinical conditions as diverse as cystic hygroma,



**Figure 10.12** Physiologic and pathologic processes common to and linking the lymphatics with blood vessels and involving the growth of lymphatic vessels (lymphangiogenesis) analogous to and often accompanied by the growth of blood vessels (hemangiogenesis). Normally, these two vasculatures remain separate and connect directly only at a few strategic sites. In a variety of disorders, including tumor-associated angiogenesis, angiomas, Kaposi sarcoma, and angiotumorigenesis, the two vasculatures come to resemble one another, interdigitate, and even merge indistinguishably. (Modified from Witte MH, Dellinger M, Bernas M, et al. Molecular lymphangiogenesis and genetics of lymphedema-angiomyoedema syndromes. In: Földi M, Földi E, eds. *Textbook of Lymphology*. 6th ed. Munich, Germany: Urban & Fischer; 2006:497–523.)

Klippel–Trénaunay syndrome, (lymph) angiosarcoma, elephantiasis, and a constellation of peripheral and visceral disorders characterized by swelling, scarring, immunodysregulation, and malnutrition (Fig. 10.12; also see Figs. 10.1 and 10.9).

## PATHOPHYSIOLOGY

### Overview

Because both congenital absence and radical excision of regional lymph nodes (and hence, lymphatics) are associated with edema, it seems straightforward that lymphedema is simply the end result of insufficient lymphatic drainage (low-output failure of the lymphatic circulation). This scenario contrasts with the more common local or generalized edemas (high-output; see Fig. 10.7) from venous occlusion, heart failure, and hepatic cirrhosis. Despite this reasonable conclusion and its pathophysiology, peripheral lymphedema has proved both hard to reproduce experimentally and difficult to treat.

Initial experimental attempts to simulate the clinical condition by lymphatic sclerosis and radical excision were notoriously unsuccessful and revealed a remarkable capacity of obstructed lymphatics to regenerate and “bridge the gap” or bypass the induced blockage with spontaneous opening of auxiliary lymphatic–venous shunts.<sup>156</sup> Although transient swelling was common, these compensatory mechanisms precluded the development of chronic lymphedema solely based on obstruction of lymphatic drainage.

The general failure of early lymph stasis experiments to reproduce unremitting peripheral edema reinforced a long-held theory that overt or subclinical bacterial infection (lymphangitis) was indispensable for evolution of chronic lymphedema.<sup>157</sup> By disrupting microvascular integrity and promoting lymphatic obliteration, recurring infection was thought to exacerbate tissue scarring and cause unremitting lymphedema. This widely held belief was consistent with the commonly observed delayed onset and unpredictability of arm and leg edema after radical mastectomy and groin dissection,

respectively, and the grotesque deformities of tropical lymphedema (so-called elephantiasis) from filariasis (*Wuchereria bancrofti* and *Brugia malayi*).

## Lymphedema and Lymphangiodyplasia

Although understanding is still incomplete, it is now nonetheless clear that nonpitting, brawny extremity edema can arise from lymph stasis alone and by the unremitting accumulation of protein-rich fluid in the extracellular matrix. By using repeated intralymphatic injection of silica particles, Drinker et al.<sup>158</sup> first succeeded in simulating chronic lymphedema in dogs through extensive lymphatic sclerosis. Subsequently, Danese et al.,<sup>159</sup> Olzewski,<sup>95</sup> and Clodius and Altorfer<sup>160</sup> established that refractory lymphedema could result solely from mechanical interruption of peripheral lymphatics. In an experimental model of circumferential lymphatic transection, tissue swelling was found to be prompt at first (acute lymphedema), disappeared by 4 to 6 weeks, and remained absent for months to years (latent lymphedema), but thereafter reappeared and persisted (chronic lymphedema). If radiation is combined with circumferential excision, the lymphedema is more severe and persists, as shown in rodent models of secondary lymphedema.<sup>161–163</sup> A similar sequence of events occurs in experimental filariasis (caused by *Brugia malayi*).<sup>164</sup> During the latent phase, when edema is not visible, conventional oil lymphography corroborates ongoing lymphatic destruction.<sup>139</sup> Progressive truncal tortuosity and dilatation give way to massive lymphangiectasis, valvular incompetence, and retrograde flow (dermal backflow). Serial microscopy discloses mononuclear cell infiltration, intramural destruction of lymphatic collectors, and collagen deposition throughout the soft tissues. Eventually, the lymph trunks lose their distinctive smooth muscle and endothelial lining, and the boundary lines between lymph collectors and the surrounding matrix progressively blur.<sup>95,168</sup>

These studies definitively demonstrate that extensive impairment of lymph drainage is sufficient by itself to cause chronic lymphedema (see Fig. 10.9). The key observation is the long interval between disruption of the lymph trunks and the development of refractory edema, which helps to explain the unpredictability of limb swelling after radical operations for treatment of cancer and other disorders of defective lymphatic drainage. As with deep venous occlusive disease, which is associated with valve destruction, venous stasis, and eventually overt edema (post-thrombotic syndrome) with characteristic trophic skin changes (hyperpigmentation and ulceration), absence or obliteration of the lymphatic vessels is associated with lymphatic valve incompetence, lymph stasis, and eventually, intractable edema (post-lymphangitic syndrome) with its characteristic trophic skin changes (thickened toe skin folds or Stemmer sign, warty overgrowth, and brawny induration).<sup>165</sup>

Other lymphangiodyplasias were described long ago but remain poorly understood and treated. They often involve both the lymphatic and blood vascular systems and range from simple birthmarks to syndromes consisting of mixed lymphatic and venous components with benign tissue overgrowth to malignant lymphangiosarcoma (Box 10.2; also see Fig. 10.12).

### BOX 10.2

### Clinical Examples of Hemangiodyplasia/ Lymphangiodyplasia

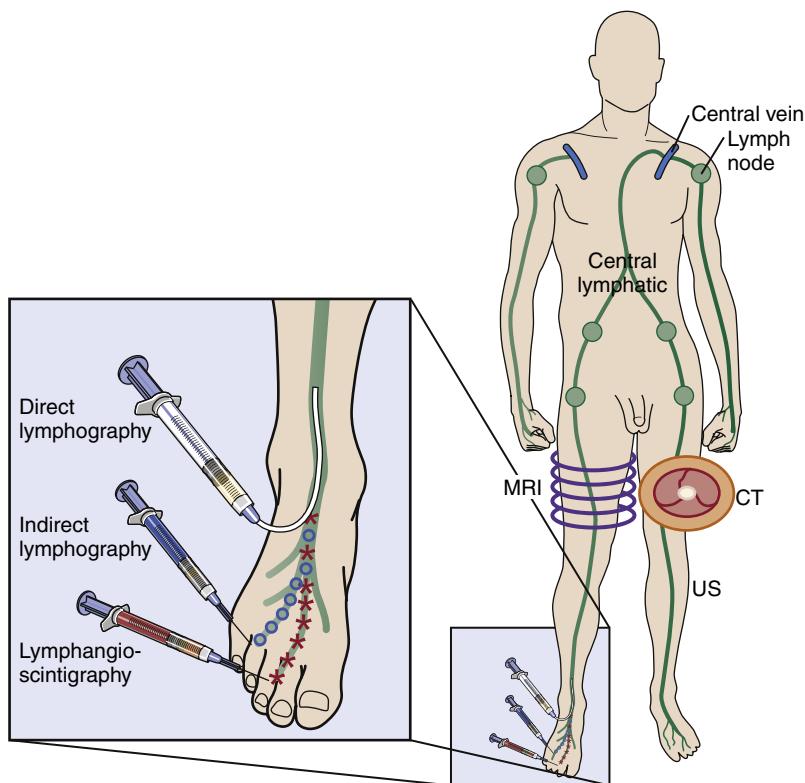
A bewildering, poorly classified constellation of angiogenic, angioproliferative, and angiotumorigenic (benign/malignant) manifestations consisting of the following:

- Vascular “birthmarks”
- Capillary, cavernous, etc., hemangiomas, lymphangiomas, and mixed angiomas
- Angiomatosis, including “benign metastasizing” lymphangioma
- Histiocytoid hemangioma
- Malignant endovascular papillary angiomyxoma
- Epithelioid hemangioendothelioma(tosis)
- Kaposi sarcoma, kaposiform eruptions
- (Lymph)angiosarcoma

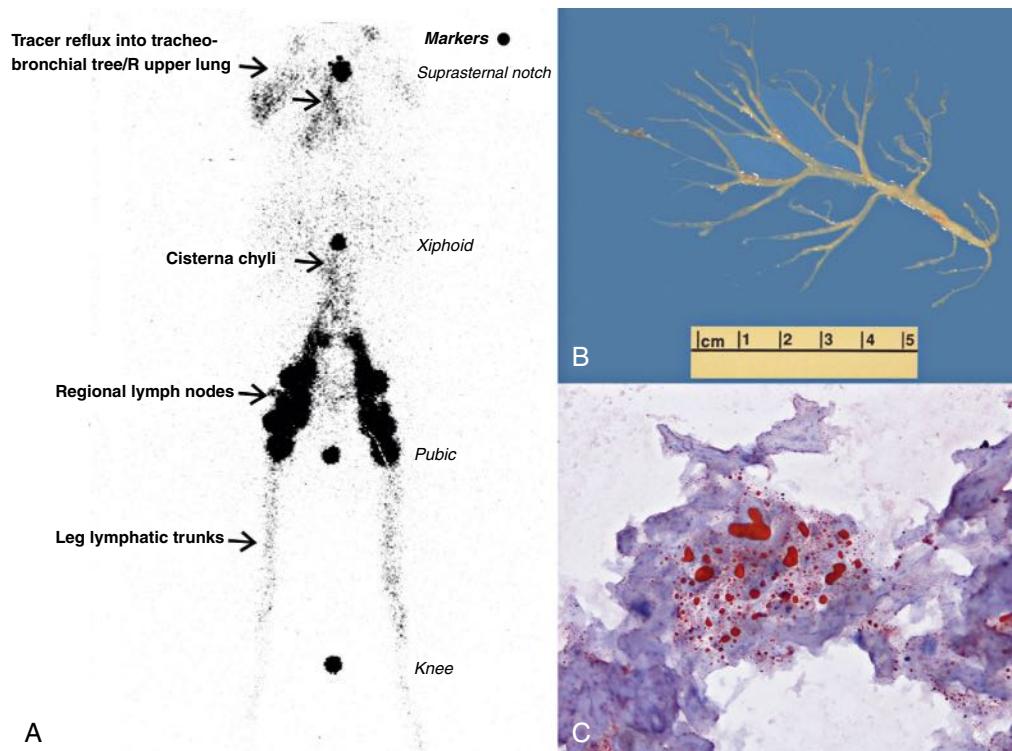
These pathologic conditions and the biochemical and/or tissue composition changes (see Fig. 10.9 and Box 10.2) can be evaluated and imaged for diagnosis, prognosis, and intervention by a variety of modalities (e.g., circumferential measurements for limb volume, bioimpedance spectroscopy for fluid measurement, tonometry for tissue hardness, CT, MRI, dual energy X-ray absorptiometry [DEXA], and ultrasound for deep and superficial tissue analysis), depending on the clinical findings (Fig. 10.13). The current “gold standard” for lymphatic system imaging is whole-body lymphangiography (Fig. 10.14).<sup>55</sup> More detailed imaging of central structures may be necessary by MR lymphangiography without and with contrast administered by intranodal, endovascular or percutaneous route with the opportunity for interventional therapy. However, for supermicrovascular surgeons, staging of degree and consequences of obstruction by ICG or photoacoustic imaging may be more helpful in defining local (not more systemic) lymphatic pathology and pathophysiology.

## Chylous and Nonchylous Reflux

Abnormal retrograde transport of lymph is termed reflux. When the lymph fluid derives from outside the intestine (e.g., from the limbs, where it is generally straw-colored to clear), it is termed nonchylous reflux, whereas lymph arising from the intestines (generally milky in color) and flowing retrograde is termed chylous reflux. The phenomena of lymph reflux was observed and recorded as far back as Cruikshank.<sup>166</sup> In 1878 Busey described patients with both chylous and nonchylous reflux syndromes with accompanying lymphedema.<sup>167</sup> Because cholesterol and long-chain triglycerides in the form of chylomicra are absorbed exclusively by the lymphatic system, dysfunction (in the form of disruption, compression, obstruction, or fistulization) of mesenteric lacteals, the cisterna chyli, and the thoracic duct is directly linked to chylothorax, chylous ascites, chyluria, chylometrorrhagia, and protein-losing enteropathy. In some patients with high-grade blockage of intestinal lymph flow, the peripheral lymphatics gradually dilate, and with progressive valvular incompetence, lactescent lymph refluxes into the soft tissues of the pelvis, scrotum, and lower extremities (chylous vesicles and chyledema) or even into the bronchial tree, manifesting as chyloptysis (see Fig. 10.14). Transgenic



**Figure 10.13** Techniques used for structural and functional imaging of the lymphatic system include direct lymphography with an oily contrast agent directly instilled into a lymphatic vessel and indirect lymphography with color vital dyes, fluorescent particles, or radioactive isotope (lymphangioscintigraphy) injected intradermally. Other useful techniques include magnetic resonance imaging (MRI), computed tomography (CT), and ultrasound (US), including photoacoustic refinements.



**Figure 10.14** Chylous Reflux Syndrome Manifesting as Chyloptysis in an 11-Year-Old Boy with Congenital Heart Disease Following Fontan Repair. (A) Bilateral lower extremity technetium 99m sulfocolloid lymphangioscintigram. Note prompt cephalad tracer transport from foot injection sites into peripheral and central lymphatic trunks and regional inguinal and retroperitoneal lymph nodes up to the level of the cisterna chyli with demonstrable retrograde reflux of tracer (arrow) into the tracheobronchial tree and right upper lung field. Radioactive markers placed at key anatomic landmarks: knee, pubic, xiphoid, and suprasternal notch. (B) Large arboreal bronchial cast preserved following expectoration. (C) Acellular cast with oil red O positive lipid droplets, original magnification  $\times 200$ . (Modified from Parikh K, Witte MH, Samson R, et al. Successful treatment of plastic bronchitis with low fat diet and subsequent thoracic duct ligation in child with Fontan physiology. *Lymphology*. 2012;45(2):47–52.)

(particularly the angiopoietin-2 knockout mouse),<sup>168</sup> radiation-induced,<sup>163</sup> and spontaneously arising mouse models with chylous effusions are available to further study these chylous reflux syndromes (see Table 10.2). Dynamic imaging of both chylous and nonchylous lymph reflux can usually be accomplished by adjusting the whole-body protocol for lower, and rarely, upper limb lymphangiography and can be applied in newborn infants to adults to identify the source, timing, and locations of the lymph reflux (see Fig. 10.14).<sup>55</sup> Increasingly, life-threatening chylous reflux has occurred in children with complex cardiac anomalies such as single ventricle related clearly to the elevated central venous pressure needed to keep surgically constructed cardiovascular shunts open. Attempts to image clearly and correct the lymphatic overload/obstruction through surgical or interventional endovascular stent shunt grafting are aimed at thoracic duct decompression by bypassing resistance at the cervical lymphatic–venous junction to excess lymph formation from elevated central venous pressure or, in hepatic cirrhosis, from portal hypertension.

## Infection

Recurrent cellulitis can be a devastating sequela of peripheral lymphedema. Erysipelas resulting from  $\beta$ -hemolytic streptococcal infection is most common, but fulminant infection occurs with a variety of microorganisms.<sup>169</sup> Patients with lymphedema (in contrast to edematous states arising from imbalances in transcapillary hydrodynamic forces) are so prone to recurring dermatolymphangitis that at one time it was mistaken as the *sine qua non* of lymphedema.

The reasons for extraordinary susceptibility of a lymphedematous extremity to bacterial infection remain perplexing. Studies of canine-induced and human filarial lymphedema implicate defective complement activation and immunodysregulation.<sup>170</sup> In addition, dampened monocyte function has been reported in microfilaremic patients.<sup>170</sup> Alternative hypotheses include depopulation of regional lymph nodes with replacement by fat and scar<sup>47</sup> and deficient protease activity of extra-vascular macrophages.<sup>171</sup> Notwithstanding, the onset of overt lymphedema is often precipitated by sudden infection or injury in an extremity already exhibiting defective lymphatic function. This initiates a protracted pernicious cycle that in the extreme culminates in a pachyderm-like deformity, and on rare occasion, leads to a highly aggressive vascular malignancy (see Fig. 10.9). Some strategies for bacterial and/or fungal prophylaxis, particularly in endemic filarial regions, have been undertaken. However, the value of long-term prophylaxis in Western and/or nontropical countries (demonstrating lower rates of infections) has not been well studied, nor has prophylaxis been widely practiced. But it does appear that control of the lymphedema itself through operative or nonoperative measures can reduce the incidence of recurrent infection.

## Fibrosis

Like the sequelae of superimposed infection, the complications of progressive interstitial fibrosis also set lymphedema apart from

other edematous states. Although the pathogenetic sequence is still unclear, it has long been recognized that conditions associated with edema high in protein content (e.g., lymphedema) are characterized by fibrous proliferation and propagation of other cell types, including adipocytes. Altered cytokine production, perturbed immunoreactivity, accumulation of abnormal complexed plasma protein moieties, including growth factors in the extracellular matrix, proliferation of mast cells with release of vasomediators such as histamine,<sup>172,173</sup> alteration in the matrix sol-gel state, and activation of a complement cascade with “fixation” to immunocomplexes. The aforementioned alterations may exert their influence, singly, or through both microvascular and chemotactic effects, to facilitate cell mobility and tissue infiltration of chronic inflammatory cells (e.g., lymphocytes and macrophages).<sup>174</sup> As fibrin- and cell-binding circulating fibronectins accumulate in the stagnant edema fluid, they act as the scaffolding and support glue for the migration of fibroblasts and deposition of collagen.<sup>175</sup> In addition, lymph stasis and the build-up of plasma proteins trapped in the interstitium overwhelm intrinsic neutrophil and macrophage proteases and provoke diffuse scarring.<sup>176</sup>

## Adipogenesis

Although the connection between the lymphatic system and fat absorption and/or deposition has been recognized by clinicians for well over a hundred years, the subject received relatively little interest until publications suggested mechanisms. It has long been recognized that a lymphedematous limb accumulates fat at an increased rate in comparison with the rest of the body and that, conversely, when weight loss is undertaken, the lymphedematous limb loses fat at a slower rate than the body does. The reasons for these observations are not understood. A report and accompanying comment studying Prox1 haploinsufficient mice proposed that lymph itself is stimulatory to fat cells.<sup>177,178</sup> More recent studies using the mouse tail have reported that lymph stasis stimulates adipogenesis and upregulation of fat differentiation genes.<sup>179,180</sup>

In humans, it is known that adipogenesis occurs both prenatally and postnatally (particularly in relation to the modern lifestyle of excessive caloric consumption and epidemic obesity).<sup>181</sup> Obesity also can lead to significant changes in the skin, microcirculation, collagen structure and function, and lymphatics.<sup>182</sup> In humans, there is evidence that the presence of static lymph itself can also influence localized adipocyte hypertrophy.<sup>183</sup>

Adipocytes vary in function and growth potential. The fat pads on the soles of the feet rarely enlarge, whereas those in the midsection can enlarge greatly in number and size. These distinct regions also are likely to have different profiles of cytokine production and growth factors in response to the local environment and in turn to influence it. A factor from human preadipocytes has been shown to preferentially stimulate lymphatic endothelial cell growth *in vitro*,<sup>184</sup> and other work in rabbits has demonstrated that preadipocytes differentiate more completely when lymph is added to the culture medium.<sup>185</sup> In addition, multipotent mesenchymal stem cells give rise to adipocytes (as well as bone, muscle, and cartilage).<sup>186</sup>

The permanent accumulation of large amounts of fat in limb lymphedema is a poor prognostic factor for physical treatment methods and has given rise to therapeutic approaches such as liposuction to directly remove the fat.<sup>187</sup>

## Lymphatic Tumors and Tumor Lymphatics

A rare but revealing sequela of long-standing peripheral lymphedema is the occurrence of lymphangiosarcoma and/or angiosarcoma and perhaps also other opportunistic neoplasms. This aggressive vascular malignancy was once thought to arise exclusively after radical mastectomy and irradiation for local control of breast cancer (Stewart–Treves syndrome).<sup>188,189</sup> However, lymphangiosarcoma has now been documented in other secondary lymphedemas and even in congenital or primary lymphedema.<sup>190</sup> Because preexisting swelling has usually persisted for many years and may occur in either primary or secondary lymphedema or in the presence or absence of previous radiotherapy, the lymphedema process itself has been thought to be the prime cause. More recently, Kaposi sarcoma, a vascular tumor akin to Stewart–Treves syndrome and allied closely with AIDS, has been linked to an origin from virally transformed lymphatic endothelium.<sup>191–194</sup> Perhaps immunodysregulation underlies a wide range of common and bizarre vasoproliferative and lymphologic syndromes, including hemolymphangioma (representing “angiotumorigenesis”), Klippel–Trénaunay syndrome, Gorham–Stout syndrome and MLA (bony lymphangiomatosis or “disappearing bone disease”), angiofollicular hyperplasia (epithelioid hemangioma), lymphangioleiomyomatosis, Kaposiform hemangioendotheliomatosis, and tumor lymphangiogenesis and lymphangitic metastatic carcinomatosis (see Fig. 10.12).<sup>195,196</sup> Specific genes have been identified in the RAS and MAPK pathway that underlie some of the lymphatic malformations and directed gene therapy has been reported to be effective in controlling and even reversing the condition.<sup>197</sup> In addition the role of lymphatic obstruction in the genesis of the malformations and of central lymphatic decompression in reversing it is another approach to the problem in addition to debulking of the tumors which may lead to long-term survival providing uncontrolled chylous leaks do not dominate the condition and become the immediate cause of death. These leaks can often be controlled now by interventional image-guided sclerosis or gluing of the leak points in the central lymphatic system.<sup>82,83</sup>

Tumor angiogenesis, which generally refers to hemangiogenesis, has been extensively studied since Folkman's original observations<sup>198</sup> and has also become a major therapeutic target, including a target of blockbuster drugs such as Genentech's bevacizumab (Avastin).<sup>199,200</sup> Tumor lymphangiogenesis,<sup>201</sup> a phenomenon whose very existence until recently was questioned, has now become a hot topic. Yet cells giving rise to the two vasculatures overlap and may interchange in specific pathologic settings and resemble each other more in regional settings. Now, various biotechnology companies, stimulated by thought leaders in the angiogenesis field, are vigorously pursuing pharmaceuticals with antilymphangiogenic properties and

testing them in preclinical models for application to patients with cancer.<sup>195,196,199,202</sup>

## Other Lymphangiogenic Disorders

Although the specific disturbances in lymphangiogenic processes have not been pinpointed for a variety of syndromes and disorders, likely lymphatic growth and remodeling initiating or secondary events are affected in inflammation, infection, and immunodysregulation. In primary disorders such as lymphangioleiomyomatosis, lymphangiectasia, and lymphangiomas, the lymphatic disturbances are clear, but their lymphatic structural and functional details, range of clinical phenotypes, and molecular bases have not been well delineated.

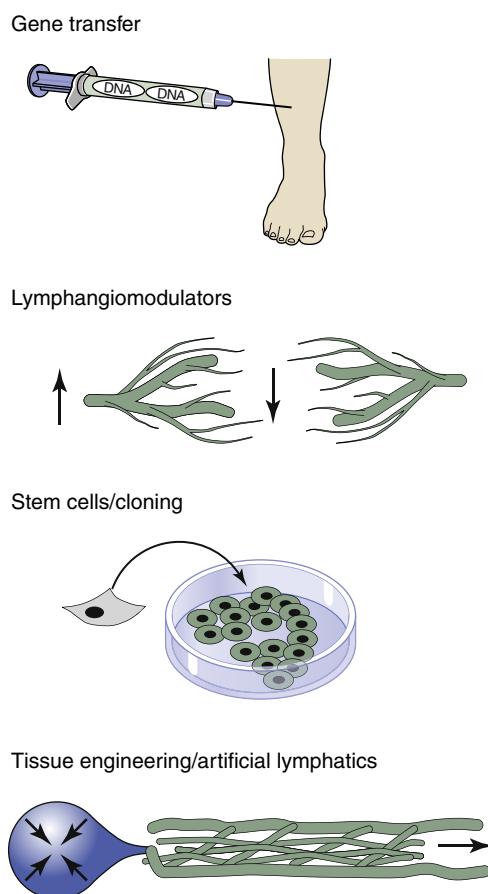
## CLINICAL SUMMARY

Disturbances in microcirculatory perfusion and exchange of liquid, macromolecules, and cells across intact and abnormal microvessels and deranged lymphatic growth patterns and lymph kinetics are, individually and together, associated with disorders of tissue swelling. Low-output failure of the lymph circulation manifested as peripheral lymphedema is characteristically indolent for many years before lymphatic insufficiency and tissue swelling accelerate and become persistent. Nonetheless, impedance of lymph flow by itself is sufficient to explain at least mild to moderate forms of lymphedema. Chronic lymphedema is characterized by trapping of fluid and extravasation of plasma proteins and other macromolecules in the skin and subcutaneous tissues. It is typical to find impaired immune cell trafficking (lymphocytes, Langerhans cells, monocytes), abnormal transport of autologous and foreign antigens, probably intact hydrodynamic (Starling) transcapillary forces,<sup>203,204</sup> and an increased propensity for superimposed infection. Additional characteristics include progressive obliteration of lymphatics (lymphangiopathy “dieback” or lymphangitis), defective lymphangion contractility, mononuclear cell infiltrates (chronic interstitial inflammation), epidermal cell-fibroblast proliferation, collagen deposition, altered immunoreactivity, and vasoactive mediator imbalance with increased production of local cytokines and growth factors, including autocrine and paracrine hormones.

On the other hand, still more common is lymphatic overload (high output failure of the lymph circulation) as occurs in hepatic cirrhosis with portal hypertension and in right heart failure.<sup>205</sup> Lymphatic overload is approached therapeutically by restoring lymph balance by either reducing excess lymph formation or accelerating lymph absorption or both. Events at the thoracic-duct venous junction (central venous hypertension or pincock effect from limited distensibility) may be critical in interfering with the free flow of overproduced lymph where thoracic duct decompression may be beneficial.<sup>206–209</sup>

Transdifferentiation and transformation of endothelium and other vascular accessory cells associated with lymph stasis may also be pivotal factors in a wide range of dysplastic and neoplastic vascular disorders, including Stewart–Treves syndrome, AIDS-associated Kaposi sarcoma, recurrent lymphangiomatosis, and

lymphangitic metastatic carcinomatosis. These phenomena have their origin in controlled and uncontrolled lymphangiogenesis and apparently are regulated at specific sites across the genome. Their manipulation may offer new avenues of therapy for both primary and secondary lymphedema and related angiomyeloma syndromes, as well as a variety of neoplasms. These new approaches include gene therapy to supply the normal gene and angiomyeloma therapy to promote lymphangiogenesis when inadequate (as in lymphedema) or inhibit lymphatic growth when excessive (as in lymphangioma). Stem cell therapy to grow new vessels from undifferentiated embryonic or adult stem cells (e.g., lymphangioblasts) and new biomaterials for artificial lymphatics and scaffolding to drain the tissues also hold promise for the future (Fig. 10.15).



**Figure 10.15** Future approaches to the treatment of patients with lymphedema-angiomyeloma disorders may include gene and/or protein transfer, modulation of growth and/or inhibitory factors, “reprogramming” with stem cells, or artificially engineered vessels/systems. (Modified from Witte MH, et al. Molecular lymphangiomyeloma and genetics of lymphedema-angiomyeloma syndromes. In: Földi M, Földi E, eds. *Földi's Textbook of Lymphology*. 3rd ed. Munich, Germany: Urban & Fischer; 2012:444–466.)

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# Diabetes

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Diabetes is characterized by chronic hyperglycemia resulting either from a lack of insulin production (type 1) or from insulin resistance (type 2). In the past several decades an alarming rise in the global prevalence of diabetes has been seen. The cost to the healthcare system is enormous because the medical expenditures of people with diabetes are 2 to 3 times higher than those of the rest of the population. In 2017, the total cost of diabetes in the United States alone was estimated at \$327 billion, including \$237 billion in direct medical costs and \$90 billion in indirect costs due to disability, work loss, and premature death.<sup>1</sup>

The health consequences of diabetes are primarily vascular and are routinely divided into microvascular and macrovascular categories. The most important microvascular complications are retinopathy and nephropathy; people with diabetes have a 20-fold increased relative risk of blindness and a 25-fold higher relative risk of end-stage renal disease compared with people without diabetes. Macrovascular disease is characterized by atherosclerosis.<sup>2</sup> Diabetes is an important risk factor for the development and severity of all forms of atherosclerosis, including peripheral artery disease (PAD), coronary artery disease (CAD), and cerebrovascular disease (CVD). Most of the 270,000 diabetes-related deaths in the United States every year

are due to CAD.<sup>1</sup> Diabetes also increases the risk of ischemic stroke twofold to threefold and accounts for 60% of nontraumatic lower-limb amputations.<sup>3–7</sup> These financial and physical costs are expected to increase in the next few decades as the prevalence of diabetes continues to rise worldwide.

## EPIDEMIOLOGY

Over the past several decades, the global prevalence of diabetes has nearly quadrupled, with an estimated 425 million people worldwide currently diagnosed with the condition. This number is predicted to exceed 629 million by 2045.<sup>8</sup> In the United States 10.5% of the population, or 34.2 million people, have diabetes and 88 million people have prediabetes (characterized by insulin resistance). Although the prevalence of diabetes is shifting to a younger demographic as the overall population becomes more obese, the risk of diabetes continues to increase with age, and as many as 26.8% of all Americans over the age of 65 have diabetes. The prevalence rate is highest for American Indians/Alaska Natives (14.7%), followed by Hispanics (12.5%) and non-Hispanic Blacks (11.7%), and lowest for non-Hispanic Asians (9.2%) and non-Hispanic Whites (7.5%).<sup>1</sup>

Global demographic changes and lifestyle factors that directly affect the incidence of diabetes are the major contributors to the increasing prevalence of diabetes worldwide. More than one-third of the increase in number of persons with diabetes worldwide over the past few decades can be attributed to increases in population size and aging of populations. Lifestyle changes related to increasing industrialization and economic development, and the interaction between demographic changes and lifestyle factors explain the remainder of this trend.<sup>9</sup> Industrialization has led to both the abundance of cheap high-calorie food and adoption of a sedentary lifestyle in the same countries with the greatest population growth, leading to an epidemic of obesity worldwide. Among persons with diabetes in the United States, an estimated 89% are overweight or obese.<sup>1</sup>

## CLASSIFICATION OF DIABETES

### Type 1

Type 1 diabetes is characterized by an absolute deficiency in insulin secretion and accounts for 5% to 10% of diabetes diagnoses.<sup>10</sup> It results from cellular-mediated autoimmune destruction of the pancreatic beta cells and requires both genetic and environmental factors to cause the disease state. Markers of immune destruction of the beta cell are present in 70% to 90% of patients and can aid in the diagnosis. These include islet cell autoantibodies, autoantibodies to insulin, antiglutamic acid decarboxylase antibodies, and autoantibodies to tyrosine phosphatase IA-2 and IA-2 $\beta$ .<sup>11</sup>

Typically, type 1 diabetes presents with acute hyperglycemia or ketoacidosis as the first disease manifestation. Type 1 diabetes (previously known as “juvenile-onset” diabetes) often presents in children and adolescents but can present at any age. It also frequently develops in patients who have other autoimmune diseases such as lupus, rheumatoid arthritis, and Hashimoto thyroiditis.<sup>10</sup> Because patients with type 1 diabetes have an absolute deficiency in insulin secretion, their treatment is reliant on insulin replacement therapy.

### Type 2

Type 2 diabetes results from a combination of insulin resistance and inadequate compensatory insulin secretion, accounting for 90% to 95% of patients with diabetes.<sup>10</sup> Although type 2 was previously referred to as either “adult-onset” or “noninsulin-dependent” diabetes, these terms are less accurate because many patients may require insulin treatment and because it can develop at practically any age. In the United States more than 20% of new diagnoses of diabetes in people under the age of 20 are due to type 2.<sup>1</sup>

The pathogenesis of type 2 diabetes is heterogeneous, with both environmental and genetic causes. Obesity is strongly related to insulin resistance and is the most important environmental factor. The heritability of insulin sensitivity is approximately 40%.<sup>12</sup> Although insulin resistance is clearly necessary for the development of type 2 diabetes, incomplete

compensatory rise in insulin secretion (relative deficiency) must also be present for hyperglycemia to result. This concept was illustrated by DeFronzo, who demonstrated that plasma insulin response to ingested glucose increases progressively in individuals who have fasting glucose concentration less than 120 mg/dL. Having a fasting glucose greater than 120 mg/dL is progressively associated with a corresponding decline in insulin secretion.<sup>13</sup> Genomic studies have identified more than 88 gene loci associated with the risk of developing type 2 diabetes. Most of these loci are primarily associated with insulin secretion and beta cell function, with few genes (e.g., *NAT2*) linked to insulin resistance that is independent of obesity.<sup>14</sup> In type 2 diabetes the hyperglycemia tends to develop slowly, and therefore the symptoms are more subtle. These include polyuria, polydipsia, weight loss, and polyphagia. Because people with type 2 diabetes have varying levels of insulin resistance and deficiencies in insulin secretion, they require the titration of different medications to achieve appropriate glycemic control.

## DIABETES AND VASCULAR DISEASE

Vascular disease is the most significant cause of morbidity and mortality in people with diabetes.<sup>3</sup> There is a direct relationship between sustained hyperglycemia and disease severity in microvascular diseases such as retinopathy, nephropathy, and neuropathy; thus these diseases are more prominent in type 1 diabetes, with its long duration of hyperglycemia exposure.<sup>3</sup> On the other hand, glycemic variability has a more deleterious effect on macrovascular complications such as CAD, PAD, and CVD.<sup>15</sup>

### Coronary Artery Disease

Diabetes is associated with a significantly increased risk of developing CAD, and patients with diabetes and CAD have been shown to have worse outcomes. People with diabetes tend to present with CAD at a younger age than patients without diabetes. It is estimated that diabetes leads to clinically evident CAD as much as 15 years earlier than otherwise expected.<sup>16</sup> Once diagnosed with CAD, persons with diabetes have a higher risk of cardiovascular death, recurrent myocardial infarction (MI), stroke, and coronary stent thrombosis.<sup>17</sup> Furthermore, people with diabetes account for a disproportionate number of those presenting with acute coronary syndromes.<sup>18</sup> Following MI, people with diabetes have higher rates of morbidity and mortality, with a 58% higher mortality than in nondiabetics at 30 days<sup>19</sup> and nearly 50% higher mortality at 1 year.<sup>20</sup>

### Cerebrovascular Disease

Diabetes is associated with at least twice the risk for stroke, a 2-year earlier age of onset of CVD symptoms, and worse functional outcomes compared with nondiabetics.<sup>18</sup> The duration of diabetes, but not the quality of glycemic control, is an independent predictor for risk of ischemic stroke. For patients treated with thrombolytic therapy for acute stroke, hyperglycemia is associated with a higher failure of recanalization and

increased risk for hemorrhagic conversion.<sup>21</sup> After a completed stroke, diabetes doubles the risk for a recurrent event.<sup>22</sup> Although stroke is responsible for 20% of mortalities among people with diabetes, no significant difference has been demonstrated in the mortality rate after stroke among diabetics compared with nondiabetics. Among diabetic survivors of ischemic stroke, half will have long-term disability and are less likely than nondiabetics to be discharged home and are more likely to suffer loss of independence in the short and long term (3, 6, and 18 months).<sup>22</sup>

## Peripheral Artery Disease

An estimated 8.5 million Americans are affected by PAD, and more than 80,000 are hospitalized each year for the condition.<sup>23</sup> In patients with diabetes the prevalence of PAD may be as high as 40%.<sup>24</sup> In patients with diabetes, risk of PAD is increased by older age, smoking, duration of diabetes, degree of diabetes control, and presence of peripheral neuropathy. The risk of PAD is also known to be higher in African Americans and Hispanic Americans with diabetes.<sup>5</sup>

Diabetes significantly increases both the incidence and severity of limb ischemia because of several associated factors.<sup>25</sup> Insulin resistance is independently associated with PAD, after adjustment for demographic factors and medical comorbidities.<sup>26</sup> The distribution of PAD is different in patients with diabetes compared with those without it. Patients with diabetes and PAD tend to have involvement of the more distal arteries, particularly the popliteal and tibial arteries, making limb-salvage revascularization more challenging.<sup>5,6</sup> The neuropathy that often develops in people with diabetes presents several additional challenges. First, decreased proprioception and pain sensation due to sensory neuropathy reduces the ability to avoid injury by decreasing normal sensation and withdrawal to pain and may blunt rest pain symptoms of advanced ischemic disease leading to delay in diagnosis.<sup>6</sup> Second, diabetic peripheral neuropathy also leads to limited joint mobility due to motor neuropathy which fosters the formation of swan-neck foot deformity, resulting in disproportionate increases in pressure points to the metatarsal heads and other parts of the foot, making ulceration more likely.<sup>27,28</sup>

As a result, diabetes is the most common cause of nontraumatic lower extremity amputation in the United States, accounting for 55% of amputation-related hospitalizations.<sup>29</sup> In 2016 alone, diabetes was responsible for 130,000 hospitalizations for lower extremity amputation.<sup>1</sup> For people 65 to 74 years old, the risk of amputation is increased more than 20-fold compared with those without PAD and diabetes.<sup>30</sup> The combination of PAD and diabetes is of additional clinical importance given its association with cardiovascular events. Patients with both diabetes and PAD are at extremely high risk of adverse cardiovascular events. In the Linz Peripheral Arterial Disease (LIPAD) study, the mortality rate from cardiovascular disease over a 10-year period was 5% for people with diabetes, 14% for those with PAD, and 31% for patients with both.<sup>31</sup> The mortality for patients with diabetes and PAD who require a lower extremity amputation is 50% at 2 years.<sup>24</sup>

## PATHOPHYSIOLOGY OF VASCULAR DISEASE IN DIABETES

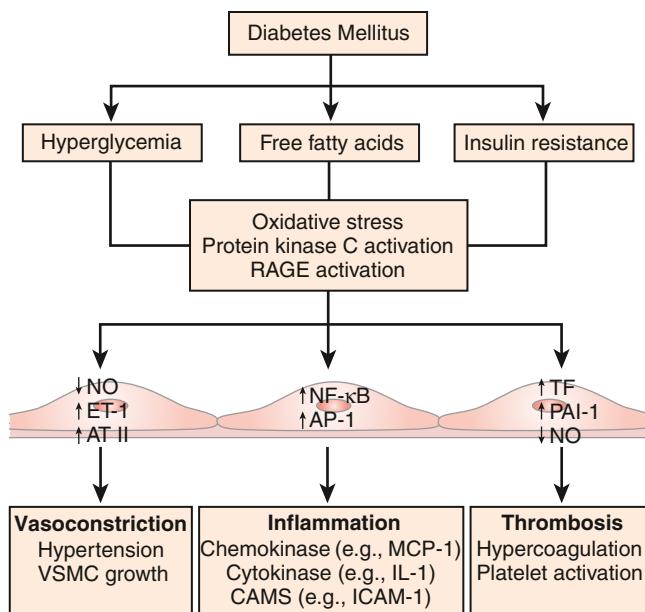
Diabetes leads to increased atherosclerotic vascular disease by a number of mechanisms, including metabolic derangements, hypercoagulability, inflammation, vascular dysfunction, and neuropathy. These alterations result in a phenotypic change in the blood vessel from one of homeostasis to an atherogenic phenotype characterized by endothelial cell dysfunction, oxidative stress mediated by increased production of free radicals, and platelet hyperactivity.<sup>32</sup>

### Dysmetabolism and Endothelial Dysfunction

Endothelial dysfunction is the key mechanism that initiates the inflammatory process associated with vascular complications in diabetes.<sup>33</sup> The two fundamental derangements that initiate endothelial cell dysfunction are hyperglycemia and insulin resistance, which are both independently associated with the development of atherosclerosis and predict cardiovascular events.<sup>32</sup>

The vascular endothelium plays a fundamental role in vascular homeostasis, regulating vascular tone, platelet activity, leukocyte adhesion and diapedesis, and vascular smooth muscle cell migration and proliferation.<sup>34</sup> The endothelium regulates vascular homeostasis through the elaboration of autocrine and paracrine that modulate the structure and function of vascular cells. Nitric oxide (NO), an endothelium-derived vasodilator, is constitutively produced in healthy endothelial cells by endothelial NO synthase (eNOS). The production of NO is closely adjusted by a wide variety of chemical and biomechanical stimuli. In addition to its potent vasodilatory properties, NO reduces production of proinflammatory chemokines and cytokines through inhibition of inflammatory transcription factors, which subsequently limits platelet activation. In contrast, decreased bioavailability of NO enhances an environment of vascular injury and atherosclerosis.<sup>35</sup> NO bioavailability is reduced in animal models, and humans with hyperglycemia and insulin resistance.<sup>36–39</sup> Endothelial dysfunction, found in both hyperglycemia and impaired endothelial insulin signaling, may link insulin resistance to its heightened risk of atherosclerosis, MI, and death. Thus endothelial dysfunction participates in the development and progression of atherosclerosis and may facilitate its adverse sequelae.

The first cardinal marker of diabetes is hyperglycemia. Hyperglycemia impairs endothelial cell function by creating an imbalance between NO bioavailability and accumulation of reactive oxygen species (ROS). Hyperglycemia-induced ROS inactivates endothelium-derived NO<sup>40</sup> and reduced NO bioavailability fosters atherosclerosis and predicts a heightened risk of cardiovascular outcomes.<sup>41,42</sup> Hyperglycemia-induced mitochondrial generation of the superoxide anion leads to cellular mitogenic pathway activation including augmented polyol and hexosamine flux, enhanced advanced glycation end products (AGEs), increased expression of AGE receptors (RAGEs), activation of protein kinase C (PKC), and activation of nuclear factor kappa B (NF-κB).<sup>43,44</sup> AGEs binding to RAGE



**Figure 12.1** The metabolic abnormalities that characterize diabetes – particularly hyperglycemia, free fatty acids, and insulin resistance – provoke molecular mechanisms that alter the function and structure of blood vessels.

increases superoxide production that promotes macrophage-induced vascular inflammation and induces decreased eNOS expression, NO synthesis, and increased endothelin-1 (ET-1) expression further contributing to endothelial dysfunction.<sup>33</sup> The upregulation and nuclear translocation of NF-κB subunit p65 and transcription of proinflammatory genes encoding for monocyte chemoattractant protein-1 (MCP-1), selectins, vascular cell adhesion molecule-1 (VCAM-1), and intracellular adhesion molecule-1 (ICAM-1) facilitate adhesion of monocytes to the vascular wall and their translocation into the subendothelium with subsequent formation of foam cells (Fig. 12.1).

The second cardinal marker of dysmetabolism in diabetes is insulin resistance. Insulin resistance likely precedes the onset of hyperglycemia by many years. In diabetes, insulin resistance affects many tissues, including skeletal muscle, liver, adipose, and blood vessels. Insulin signaling involves two major pathways: the phosphatidylinositol-3-kinase (PI3K)-dependent and the mitogen-activated protein kinase (MAPK)-dependent pathways. The metabolic and hemodynamic effects of insulin are modulated by the PI3K-dependent activation of eNOS which promotes NO production in the homeostatic state. This is impaired in insulin resistance resulting in decreased NO production. Insulin's effects on gene expression, differentiation, and cell growth are modulated by the MAPK-dependent pathway. ET-1 secretion is increased via the MAPK dependent pathway by insulin resistance resulting in endothelial dysfunction.<sup>33</sup>

Adipose tissue is an important source of inflammatory mediators and free fatty acids (FFAs),<sup>45</sup> which are elevated in the plasma of obese patients with type 2 diabetes.<sup>46</sup> Excessive FFAs impair endothelial function by similar mechanisms and to a similar extent as glucose toxicity. FFAs induce ROS production by increasing expression of NADPH oxidases, inactivate eNOS by production of superoxide, increase vascular susceptibility to

oxidative damage by increasing intracellular concentration of glutathione, and activate the inflammatory cascade by activating NF-κB.<sup>33</sup> The atherogenic effects of insulin resistance are also due to changes in lipid profile such as high triglycerides, low HDL cholesterol, increased remnant lipoproteins, elevated apolipoprotein B (ApoB), and small and dense LDL.<sup>47</sup> Once circulating FFAs reach the liver, VLDL are assembled and made soluble by increased synthesis of ApoB. VLDL are processed by cholesteryl ester transfer protein (CETP), allowing transfer of triglycerides to LDL, which become small and dense and hence more atherogenic. Atherogenic dyslipidemia is a reliable predictor of cardiovascular risk, and its pharmacologic modulation may reduce vascular events in subjects with type 2 diabetes and metabolic syndrome.<sup>48–50</sup>

## Platelet Dysfunction and Coagulation Cascade

Platelet dysfunction has also been shown to play a role in thrombosis, complicating atherosclerotic plaque rupture in diabetes. Glycoprotein Ib and IIb/IIIa expression is upregulated in diabetes, which leads to increased amounts of von Willebrand factor and platelet-fibrin interaction.<sup>51</sup> Hyperglycemia also impairs calcium homeostasis, which alters calcium-dependent platelet aggregation and activation.<sup>52</sup> Procoagulant factors (factor VIII, thrombin, and tissue factor) are increased and endogenous anticoagulants and fibrin inhibitors (thrombomodulin, protein C, plasminogen activator inhibitor 1) are decreased in a chronic hyperglycemic state.<sup>53–56</sup> Diabetes therefore leads to increased platelet aggregation and a shift in favor of the procoagulant portion of the thrombotic cascade. These alterations contribute to the propensity not only for atherosclerosis, but also for thrombosis in pathologic plaque rupture resulting in acute coronary syndrome, ischemic stroke, and acute limb ischemia, which are known to be more common in people with diabetes.

## VASCULAR EVALUATION OF PATIENTS WITH DIABETES

The vascular evaluation of patients with diabetes is a challenge for providers and requires additional evaluation for a comprehensive assessment, particularly regarding the evaluation of neuropathy, thorough foot examination, and noninvasive physiologic testing. The examination should focus on inspection of the extremities and feet for signs of skin change, hair loss, ulceration, or increased dryness. Full sensory and motor exam should then be performed with the addition of monofilament testing plus vibration sensation (using 128-Hz tuning fork), pinprick sensation, or ankle reflexes.<sup>57</sup>

The presence of neuropathy is an important risk multiplier not seen with other risk factors. Diabetic peripheral neuropathy is characterized by a symmetric sensorimotor polyneuropathy.<sup>58</sup> It starts distally, moves proximally, and results in a typical “glove and stocking” distribution.<sup>59</sup> Motor deficits are rare in the early stages of diabetic peripheral neuropathy. Burning, tingling, and shooting pains are frequently described and are typically worse at night.<sup>59</sup> Of

note, the degree of pain and subjective symptoms are not reliable indicators of sensory nerve damage. Careful peripheral neurologic examination is recommended annually in patients with diabetes.<sup>57</sup>

The American Podiatric Medical Association and the Society for Vascular Surgery recommend that patients with diabetes have ankle-brachial index (ABI) measurements performed when they reach 50 years of age. Furthermore, patients with a prior history of diabetic foot ulcer, known atherosclerotic cardiovascular disease, prior abnormal vascular examination, or prior intervention for PAD should have a clinical examination of the lower extremities and noninvasive physiologic testing (ABI and/or toe pressures) annually.<sup>24</sup> However, one important diagnostic consideration is the increased likelihood of noncompressible tibial vessels and subsequent falsely elevated ABI results in patients with diabetes. Toe pressures and transcutaneous oximetry are more reliable in these patients as the pedal and digital vessels are usually spared.

The Wound, Ischemia, and foot Infection (WIFI) classification system is a framework for stratifying amputation risk and revascularization benefit in patients with PAD that is useful in the evaluation of diabetic foot ulcers, which is reviewed in Chapter 119, Podiatric Care of the Diabetic Foot.<sup>60</sup>

## TREATMENT OF PATIENTS WITH DIABETES AND PERIPHERAL ARTERY DISEASE

The two most important goals in the treatment of patients with PAD and diabetes are improving limb outcomes (i.e., improving claudication symptoms and preventing progression to critical limb ischemia) and decreasing morbidity and mortality from cardiovascular disease and stroke. An aggressive approach to risk factor modification and medical treatment is the cornerstone to achieve both goals. Target-driven medical intervention can reduce the risk of cardiovascular events by as much as 50% in patients with type 2 diabetes.<sup>61</sup> A sample treatment algorithm for patients with PAD and diabetes is available at the end of this chapter.

### Preventive Foot Care

Peripheral neuropathy, ischemia, and infection form the etiologic triad of diabetic foot complications.<sup>62</sup> Proper foot care and hygiene are the hallmarks of preventive therapy. Commonly, diabetic foot ulcers and infections begin as small wounds that are not recognized and treated in the early stages because symptoms may be masked by sensory neuropathy. Approximately 28% of adults with diabetes in the United States have peripheral neuropathy, and 25% will develop a foot ulcer in their lifetime.<sup>63</sup> Therefore, careful screening and early intervention are important in preventing diabetic foot complications. After development of a diabetic foot ulcer (DFU) patients have a 40% annual risk of recurrence. Duration of diabetes and diabetic neuropathy are both associated with increased risk for recurrence.<sup>64</sup> The American Diabetes Association (ADA) recommends annual foot examination to identify

high-risk conditions before complications develop.<sup>65</sup> The SVS and APMA provide more specific recommendations for prevention of diabetic foot ulceration including: (1) annual foot examination by a provider with training in foot care; (2) inclusion of the Semmes–Weinstein test for peripheral neuropathy as a component of the foot exam; (3) patient and family education about preventive foot care; (4) custom therapeutic footwear in high-risk patients, including those with significant neuropathy, foot deformities, or previous amputation; and (5) glycemic control (hemoglobin A<sub>1c</sub> <7%).<sup>24</sup> A detailed review of the treatment for DFUs is detailed in Section 16, The Diabetic Foot and Its Management.

### Glycemic Control

The study of glycemic control and the impact on macrovascular events has been investigated in three large trials performed to determine whether tight glucose control (hemoglobin A<sub>1c</sub> <6.5%) was better than standard control (hemoglobin A<sub>1c</sub> of 7%). In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, a strategy of targeting a hemoglobin A<sub>1c</sub> of 6% versus 7% to 7.9% to reduce adverse cardiovascular events was evaluated in 10,251 patients.<sup>66</sup> The study was stopped early because the intensive glucose-lowering strategy was found to increase cardiovascular mortality without reducing other major cardiovascular events. Post-trial follow-up of the study participants demonstrated a decreased rate of lower extremity amputations after 3.7 years of intensive glucose control.<sup>67</sup> The Action in Diabetes and Vascular Disease (ADVANCE) study and the Veterans Affairs Diabetes Trial (VADT) both also failed to demonstrate a reduction in cardiovascular outcomes in patients with improved glycemic control.<sup>68,69</sup> Based on the lack of success in these large trials, the ADA recommended targeting a hemoglobin A<sub>1c</sub> of 7.0%.<sup>70</sup>

In addition to lowering glucose, insulin-sensitizing agents have been studied in relation to cardiovascular events. Metformin, a biguanide, has demonstrated improvements in cardiovascular outcomes in numerous clinical trials including reduction in cardiovascular events, cardiovascular mortality, and all-cause mortality.<sup>71</sup> Thus metformin is the recommended first-line hypoglycemic agent to be used in patients with type 2 diabetes. Glucagon-like peptide-1 (GLP-1) receptor agonists have demonstrated cardiovascular benefit with reduced stroke and cardiovascular mortality in clinical trials.<sup>72</sup> In the EMPAREG outcome trial, sodium glucose cotransporter 2 (SGLT2) inhibitor treatment was associated with a 14% decrease in major cardiovascular events, 38% decrease in cardiovascular mortality, 35% reduction in hospitalizations for heart failure, and 32% decrease in all-cause mortality.<sup>73</sup> The thiazolidinediones have a mixed cardiovascular outcomes record. In the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive), pioglitazone did not demonstrate macrovascular benefits in terms of reduction of cardiovascular events at 10-year follow-up.<sup>74</sup> Rosiglitazone, on the other hand, was shown to be associated with a reduction in overall cardiovascular events and cardiovascular death in the VADT.<sup>75</sup> Table 12.1 briefly reviews the different classes of medications available to treat hyperglycemia.

**TABLE 12.1** Summary of the Most Common Oral Hypoglycemic Agents

Drug Class	Agent	Mechanism of Action	Expected A <sub>1C</sub> Reduction	Adverse Effects	Outcome Data/CV Safety Concerns
Direct Acting Insulin Sensitizer	Biguanides <i>Metformin</i>	Decrease hepatic glucose production, increase glucose uptake in muscle	≈1%–2%	Diarrhea, nausea, lactic acidosis, B12 deficiency	Improves CVD outcomes; contraindicated in decompensated or unstable HF due to risk of lactic acidosis
Direct Acting Insulin Secretagogue	Sulfonylureas <i>Glyburide</i> <i>Glipizide</i> <i>Glimepiride</i>	Bind to sulfonylurea receptors on pancreatic islet cells, cardiac K <sub>ATP</sub> stimulating insulin release	≈1%–2%	Hypoglycemia, weight gain	Hypoglycemia may precipitate ischemia or arrhythmia; cardiac K <sub>ATP</sub> channel closure may impair ischemic preconditioning
Direct Acting Insulin Secretagogue	Meglinides <i>Nateglinide</i> <i>Repaglinide</i>	Bind to sulfonylurea receptors on pancreatic islet cells, increase insulin secretion	0.5%–1.5%	Hypoglycemia, weight gain	Hypoglycemia may precipitate ischemia or arrhythmia; cardiac K <sub>ATP</sub> channel closure may impair ischemic preconditioning
Nutrient Load Reducer	α-Glucosidase inhibitors <i>Acarbose</i> <i>Miglitol</i>	Delay carbohydrate absorption from intestine	≈0.5%–0.8%	Gas, bloating	Improves postprandial glucose excursions, which are more tightly associated with CVD than fasting glucose
Direct Acting Insulin Sensitizer	Thiazolidinediones <i>Rosiglitazone</i> <i>Pioglitazone</i>	Activate the nuclear receptor PPAR-γ, increasing peripheral insulin sensitivity and reduces hepatic glucose production	≈1%–1.5%	Weight gain, edema, possible bone loss in women	May precipitate clinical HF in predisposed individual
Indirect Acting Insulin Secretagogue	Incretin modulators GLP-1 mimetics <i>Exenatide</i> <i>Albiglutide</i> <i>Dulaglutide</i> <i>Liraglutide</i>	Increase glucose-dependent insulin secretion, decrease glucagon, and delay gastric emptying, increase satiety	≈1%	Nausea, vomiting, risk of thyroid C-cell tumors	Reduces risk of stroke, MI, cardiovascular mortality, and all-cause mortality
Indirect Acting Insulin Secretagogue	DPP-4 inhibitors <i>Sitagliptin</i> <i>Saxagliptin</i> <i>Linagliptin</i> <i>Alogliptin</i>	Inhibit degradation of endogenous GLP-1, thereby enhancing the effects of incretins, increase glucose-dependent insulin secretion, decrease glucagon secretion	≈0.6%–0.8%	Urticaria, angioedema	Neutral
Indirect Acting Insulin Sensitizer	Amylin analogues <i>Pramlintide</i>	Decrease glucagon secretion and delay gastric emptying, increase satiety	≈0.4%–0.6%	Nausea, vomiting	
Insulins	Insulin <i>Regular insulin</i> <i>Glulisine</i> <i>Aspart</i> <i>Lispro</i> <i>NPH insulin</i> <i>Detemir</i> <i>Glargine</i> <i>Degludec</i>	Increase insulin supply	No limit (theoretically)	Hypoglycemia, weight gain, edema (at high doses)	Neutral
Nutrient Load Reducer	SGLT2 inhibitors <i>Canagliflozin</i> <i>Dapagliflozin</i> <i>Empagliflozin</i>	Increase urinary excretion of glucose	0.5%–1%	Genitourinary infections	Improves cardiovascular outcomes

CVD, cardiovascular disease; GIP-1, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide 1; HF, heart failure; MI, myocardial infarction.

Adapted from Inzucchi SE, et al.<sup>117</sup>

Although it has not been proven to improve PAD symptoms or amputation rates, the ACC/AHA consensus guidelines on PAD treatment also support a hemoglobin A<sub>1c</sub> goal of 7.0%.<sup>76</sup> When insulin-providing therapy was compared with insulin sensitization therapy for glycemic control in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, the insulin sensitization strategy was shown to be superior in the reduction of PAD, need for lower extremity revascularization, and lower extremity amputation.<sup>77</sup> The PROactive trial, despite failing to demonstrate an effect of pioglitazone on cardiovascular outcomes, did show a significant decrease in leg amputations at 10-year follow up (4.1% for pioglitazone compared with 5.6% for placebo).<sup>74</sup>

With so many medication classes, the choice of agent for each patient may seem daunting. The ADA published a consensus guideline for the initiation and adjustment of pharmacotherapy in 2020 to aid in these decisions. According to this algorithm, lifestyle interventions are the first step of treatment along with metformin if not contraindicated. If hemoglobin A<sub>1c</sub> is greater than 9% or lifestyle interventions and maximal tolerated dose of metformin do not achieve a hemoglobin A<sub>1c</sub> less than 7%, another medication should be added. For patients at risk for cardiovascular disease, the second agent should be one with a proven cardiovascular mortality benefit (GLP1 receptor agonist or SGLT2 inhibitor). If hemoglobin A<sub>1c</sub> is greater than 10% or glycemic control is still not achieved on dual therapy, insulin therapy should be started or intensified until goal hemoglobin A<sub>1c</sub> is achieved. The ADA therefore relegates the other oral and subcutaneous medications to a “second-tier” algorithm, which it states is appropriate in certain individualized circumstances.<sup>78</sup>

## Risk Factor Control

Aggressive risk factor modification is the cornerstone for reductions in atherosclerotic cardiovascular disease (ASCVD) events. Much of this therapy is discussed in other chapters in the text; here we provide diabetes-specific data for risk factor reduction.

### Dyslipidemia

The ACC and AHA guidelines on the treatment of blood cholesterol for primary prevention of ASCVD in diabetics strongly recommend the use of moderate-intensity statin therapy if 40–75 years of age with LDL greater than 70 mg/dL. High-dose statin therapy is recommended in this group in the presence of multiple ASCVD risk factors including duration of diabetes greater or equal to 10 years for type 2 diabetes, or greater or equal to 20 years for type 1 diabetes, diabetic neuropathy, and ABI less than 0.9. High-dose statin therapy is also recommended for those aged 20–75 years old with LDL greater than or equal to 190 mg/dL.<sup>79</sup> These recommendations are based on numerous large-scale clinical trials that have shown a significant benefit of statin therapy in patients with diabetes and elevated LDL or even average LDL.<sup>80,81</sup> In the Heart Protection Study (HPS), 3000 subjects with diabetes and without evidence of ASCVD at entry but with total cholesterol greater than 135 mg/dL were randomized to simvastatin or placebo.

A 34% risk reduction was observed in the combined endpoint of coronary heart disease, stroke, and revascularization in simvastatin-treated group.<sup>82</sup> The Collaborative Atorvastatin Diabetes Study (CARDS) enrolled participants with diabetes without evidence of ASCVD but with one other cardiovascular risk factor (hypertension, retinopathy, smoking, or microalbuminuria or macroalbuminuria) and randomized these subjects to 10 mg/day of atorvastatin versus placebo.<sup>83</sup> The mean LDL level in this trial was 117 mg/dL. The results showed a 30% reduction in the composite primary endpoint of major adverse cardiovascular events (MACE) in the atorvastatin-treated group. The most significant finding of this trial is that the benefit occurred irrespective of baseline LDL levels in both treated and placebo patients.

Many non-statin drugs have been studied in patients with diabetes who were on a maximally tolerated statin with varied results. Ezetimibe, icosapent-ethyl, and two proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, evolocumab and alirocumab, have demonstrated efficacy in clinical trials for reducing ASCVD morbidity and mortality.<sup>84–89</sup> The results of these trials are summarized in Table 12.2. On the other hand, niacin, fenofibrate, and CETP inhibitors have all been shown in large-scale clinical trials to provide no benefit beyond statins in cardiovascular risk reduction.<sup>90–92</sup>

### Hypertension

Control of hypertension has been shown in multiple studies to decrease the risk of macrovascular disease and death in patients with diabetes. Indeed, blood pressure control was the first treatment to show reductions in mortality. The efficacy of intensive blood pressure lowering strategies on MACE in patients with diabetes has been evaluated in 19 high quality randomized controlled trials. In meta-analysis, intensive blood pressure treatment (mean 133/76 mm Hg) achieved a 14% relative risk reduction for cardiovascular events and 22% relative risk reduction for stroke compared to less intensive treatment (mean 140/81 mm Hg).<sup>93</sup> In the Appropriate Blood-Pressure Control in Diabetes (ABCD) trial, when patients with PAD were specifically analyzed, a significant and dramatic reduction (38.7% compared with 13.6%) was seen in MI, stroke, and cardiovascular death in the patients in the intensive blood pressure control groups.<sup>94</sup> In response to these and other studies showing similar outcomes, the current ACC/AHA guidelines for the management of hypertension involves pharmacologic therapy if blood pressure is greater than 130/80 mm Hg with a goal blood pressure lower than 130/80 mm Hg for all adult patients with diabetes.<sup>95</sup> These lower blood pressure goals have not been universally accepted. The European Society of Cardiology and European Society of Hypertension still recommend a more permissive blood pressure target of less than 140/90 mm Hg.<sup>96</sup>

### Antiplatelet Therapy

Antiplatelet therapy is a key component of secondary prevention measures in patients with diabetes and known ASCVD. However, the role of aspirin therapy for primary prevention of cardiovascular disease is less clear. Four trials

**TABLE 12.2**

**Summary of Clinical Trials of Non-Statin Agents for Hyperlipidemia with Demonstrated Efficacy for Reduction of Atherosclerotic Cardiovascular Disease Outcomes**

Trial	Design	DM % enrolled	Primary Outcome	Results Overall	Results DM subgroup
IMPROVE-IT <sup>84,85</sup>	RCT Ezetimibe + statin vs statin in patients with recent ACS	27%	MACE (MI, CVA, hospital admission for UA, coronary revascularization, or CV death)	1.8% ARR over 7 years	5.5% ARR over 7 years
FOURIER <sup>86</sup>	RCT evolocumab + statin vs statin in patients with established CVD	37%	MACE (MI, CVA, hospital admission for UA, coronary revascularization, or CV death)	1.5% ARR over 2.2 years	No difference from overall study population
ODYSSEY OUTCOMES <sup>87,88</sup>	RCT alirocumab + statin vs statin in patients with recent ACS	29%	MACE (MI, CVA, UA, or CV death)	1.6% ARR over 2.8 years	2.3% ARR over 2.8 years
REDUCE-IT <sup>89</sup>	RCT Icosopent ethyl + statin vs statin in patients with elevated TG and high ASCVD risk	59%	MACE (MI, CVA, UA, coronary revascularization, or CV death)	4.8% ARR over 4.9 years	

ARR, absolute risk reduction; ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVA, cerebrovascular accident (stroke); CVD, cardiovascular disease; MACE, major adverse cardiovascular events; MI, myocardial infarction; RCT, randomized controlled trial; TG, triglycerides; UA, unstable angina.

have been conducted specifically in patients with diabetes (Early Treatment Diabetic Retinopathy Trial; Prevention of Progression of Arterial Disease and Diabetes [POPADAD]; Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes [JPAD]; and A Study of Cardiovascular Events in Diabetes [ASCEND]), and six trials included large proportions of patients with diabetes with a wide range of study duration and aspirin dosage.<sup>97</sup> Meta-analysis of these data suggests a modest (9%) relative risk reduction in risk for cardiovascular events and more than twofold increased risk of bleeding. While the ACC/AHA no longer recommends low-dose aspirin for primary prevention of ASCVD in adults with normal ASCVD risk, it is still recommended for primary prevention in patients with diabetes 40–70 years old when the 10-year risk of cardiovascular events is greater than 10% and the baseline risk of gastrointestinal bleeding is not increased.<sup>79</sup> The European Society of Cardiology and European Association for the Study of Diabetes recommend against routine use of aspirin for primary prevention of ASCVD in patients with diabetes but it may be considered in high-risk individuals in the absence of a contraindication.<sup>98</sup>

Numerous studies have demonstrated the benefit of antiplatelet therapy in patients with known PAD for reducing cardiovascular events. A subgroup of the Antithrombotic Trialists' Collaboration meta-analysis included 9214 patients with PAD and found a significant reduction in serious vascular events with aspirin therapy.<sup>99</sup> However, more recent data question the benefits of this therapy specifically in patients with diabetes. In the JPAD trial, patients with diabetes were randomized to low-dose aspirin (81–100 mg) versus placebo, with no reduction found in the risk of MACE.<sup>100</sup> The POPADAD trial evaluated aspirin efficacy in patients with both diabetes and PAD. The 1276 patients with diabetes and PAD (based on ABI <0.99) were randomized to low-dose aspirin plus antioxidant treatment, low-dose aspirin plus placebo, antioxidant plus placebo, or double placebo. No significant difference was seen among the four groups in death from coronary heart disease, nonfatal

MI, stroke, above-the-ankle amputation, or critical limb ischemia.<sup>101</sup>

P2Y12 inhibitors have also been evaluated for use in patients with PAD to reduce ASCVD events. In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, patients with non-ST-elevation MI, ischemic stroke, or PAD were randomized to treatment with aspirin versus clopidogrel. A subset analysis demonstrated that the 3866 patients with diabetes had a 12.5% reduction in MACE with clopidogrel versus aspirin.<sup>102</sup> In patients with symptomatic PAD in the EUCLID trial, the rate of major adverse cardiovascular events (MI, ischemic CVA, or CV death) was equivalent for monotherapy with either clopidogrel or ticagrelor, with a 1.6% rate of major bleeding after 30 months follow-up. Equivalence between the two P2Y12 inhibitors was also demonstrated within the diabetes subgroup for the primary outcome (MACE) and secondary outcome, major bleeding.<sup>103</sup>

Dual therapy with aspirin (100 mg daily) and rivaroxaban (2.5 mg twice a day) has demonstrated reduction in both major adverse cardiovascular events (MACE) and major adverse limb events (MALE) in two recent clinical trials. In the COMPASS trial, dual therapy demonstrated a reduction in adverse outcomes compared to low-dose aspirin monotherapy (5% versus 7% for MACE, 1% versus 2% for MALE) after 21 months follow-up. Major bleeding was increased in the dual therapy group compared to the aspirin group (3% and 2%, respectively). In subgroup analysis of the 44% of participants who had diabetes, dual therapy was associated with a 4% absolute risk reduction for MACE and MALE compared to aspirin alone.<sup>104</sup> The Voyager-PAD trial demonstrated a 2.6% absolute risk reduction in MACE and MALE with aspirin and rivaroxaban compared to aspirin alone in patients with PAD undergoing revascularization after 3 years. Among the subgroup of participants with diabetes, no significant difference was demonstrated in the primary outcome (MACE + MALE), but major bleeding complications were more common in diabetics in the dual therapy group compared to the aspirin monotherapy group (2.4% and 1%, respectively).<sup>105</sup>

The SVS guidelines recommend antiplatelet therapy with either aspirin 75 to 325 mg or clopidogrel 75 mg in individuals with PAD,<sup>106</sup> and suggests that monotherapy with clopidogrel or dual therapy with low-dose aspirin and rivaroxaban should be considered in patients with critical limb-threatening ischemia.<sup>107</sup>

## Medical Treatment for Symptomatic Improvement of Peripheral Artery Disease

After a diagnosis of PAD has been made, therapies to preserve exercise tolerance and improve symptoms should be initiated. Exercise therapy is the most beneficial intervention for these goals, and cilostazol may also improve exertional capacity and symptoms. Medical management of symptomatic PAD is presented in detail in Chapter 108, Lower Extremity Arterial Disease: Decision Making and Medical Treatment. Diabetes-specific data for these treatments are discussed here.

### Exercise Therapy

Exercise therapy is effective in improving glycemic control and endothelial function in diabetes. Randomized controlled trials of exercise in diabetes demonstrate overall improvement in flow-mediated dilation, a marker of endothelial function, with all types of exercise. The greatest improvements are found with combined aerobic and resistance programs, followed by resistance exercise, with the least improvement demonstrated with aerobic exercise alone.<sup>108</sup> In patients with intermittent claudication, randomized controlled trials of supervised and home exercise training programs have repeatedly supported benefits, including increasing the distance to onset of claudication and increasing the distance to maximum claudication pain.<sup>109–111</sup> The GOALS trial, a home-based walking exercise intervention for patients with PAD, is the only study that reported results specifically among diabetic participants. In subgroup analysis, after a 6-month walking program, participants with diabetes significantly improved walking distance, by 46 m compared to those with diabetes in the control group, where a decrease in walking distance of 11 m was demonstrated in the same period.<sup>112</sup> The SVS recommends a supervised exercise program as the initial treatment modality for patients with intermittent claudication consisting of walking a minimum of 3 times per week (30 to 60 min/session) for at least 12 weeks or a home-based exercise program of similar intensity when a supervised exercise program is unavailable or has been completed.<sup>106</sup>

### Cilostazol

Cilostazol is a phosphodiesterase-3 inhibitor that has vasodilator, antiproliferative, and antiplatelet effects.<sup>113</sup> Although it has not been shown to have any effect on mortality, it improves symptoms of claudication in approximately 50% of patients with and without diabetes.<sup>114,115</sup> O'Donnell et al. specifically evaluated the effect of cilostazol on claudication in patients with diabetes, and demonstrated improved absolute walking distance at 6 and 24 weeks in the treatment group.<sup>116</sup> The SVS guidelines for treatment of PAD state that a 3-month trial of cilostazol at a dose of 100 mg twice daily is recommended to alleviate symptoms and improve walking distance in patients with lifestyle-limiting symptoms who do not have congestive heart failure.<sup>106</sup>

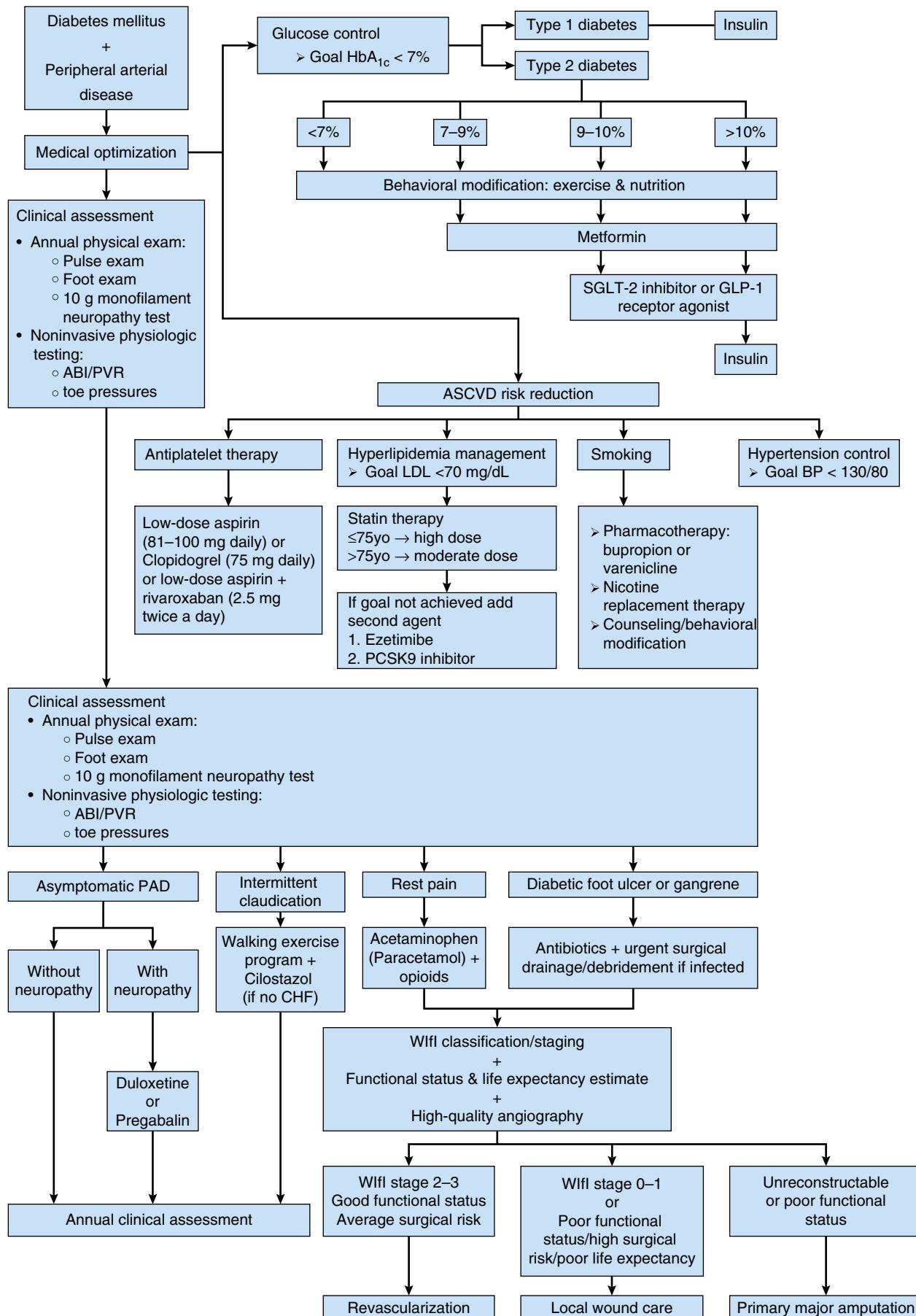
## Referral for Revascularization

When medical therapy fails, revascularization (either surgical or percutaneous) may be necessary. Indications for peripheral revascularization procedures for PAD are the same in patients with and without diabetes. In PAD, these include disabling claudication, critical limb ischemia (rest pain or tissue loss), or nonhealing or infected foot ulcers that are expected to benefit from revascularization, which is reviewed in Chapter 108, Lower Extremity Arterial Disease: Decision Making and Medical Treatment.

## SUMMARY AND FUTURE DIRECTIONS

Diabetes increases the risk of vascular disease, including cardiovascular, cerebrovascular, peripheral vascular, and microvascular diseases. CAD is responsible for the majority of the deaths in patients with diabetes, but stroke, claudication, critical limb ischemia, DFUs, retinopathy, and nephropathy all contribute to the overall healthcare expenditures and morbidity in patients with diabetes. Numerous metabolic, thrombotic, and vascular derangements occur in diabetes and explain the accelerated atherosclerosis and increased rate of thrombosis characteristic of diabetic vascular disease. Treatment of PAD in patients with diabetes involves therapies to improve claudication symptoms and aggressive risk factor modification aimed at improving cardiovascular outcomes and overall mortality. As the worldwide incidence of diabetes grows, these complications will become more and more important to global healthcare delivery.

## CHAPTER ALGORITHM



Treatment Algorithm for Peripheral Arterial Disease in Patients with Diabetes

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# Hyperlipidemia

M. ASHRAF MANSOUR

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Cardiovascular disease is the leading cause of death in industrialized countries and accounts for over 31% of deaths globally.<sup>1</sup> Over the last century, a multitude of discoveries and intense research have elucidated the mechanisms of atherosclerosis, a word derived from the Greek *atheros*, meaning gruel and *sclerosis*, meaning hard. It has been well established, for over six decades now, that the major atherosclerotic risk factors include hyperlipidemia, hypertension, cigarette smoking, and a positive family history of the disease.<sup>2–4</sup> Diabetes mellitus, obesity, lack of exercise, and poor dietary habits can also be added to the previous list (Box 13.1). At the molecular level, hypercholesterolemia and inflammatory cells play a key role in the development of the atherosclerotic plaque.<sup>5,6</sup> Numerous large-scale studies have confirmed that lowering low-density lipoproteins (LDL) levels by 30% to 50% will significantly reduce cardiovascular mortality. Between 1980 and 2000,

therapeutic cholesterol reduction has decreased mortality from atherosclerotic cardiovascular disease (ASCVD) by one third. Every few years, the American College of Cardiology (ACC) and the American Heart Association (AHA) publish guidelines and recommendations for lipid management in asymptomatic and symptomatic patients. The focus of this chapter is on the pathophysiologic role of hyperlipidemia in causing atherosclerosis, the physiology and metabolism of lipids, and the diagnosis and management of hyperlipidemia, as well as an update to the most recently published guidelines.

## **HISTORICAL PERSPECTIVE**

The notion that dietary fat had something to do with atherosclerosis has existed for some time. In 1910, a German scientist found that human aortic plaque had 25 times more cholesterol

**BOX 13.1****A Century of Cholesterol and Coronaries****First Half – The Era of Cholesterol**

1910 Human and atherosclerotic plaques contain cholesterol  
 1913 High cholesterol diet causes atherosclerosis in rabbits  
 1919 Heart attacks recognized in humans  
 1933 Feedback inhibition of cholesterol synthesis demonstrated  
 1938 Familial hypercholesterolemia described  
 1950 Cholesterol biosynthetic pathway elucidated  
 1951 High-fat diets raise plasma cholesterol in humans  
 1953 Risk factor concept advanced

**Second Half – The Era of LDL**

1955 LDL identified as risk factor for CHD  
 1973 LDL receptor discovered  
 1976 HMG CoA reductase inhibitors (statins) discovered  
 1981 Statins increase LDL receptors *in vivo*  
 1987 First statin (Mevacor) approved for human use  
 1994 Statins decrease heart attacks and prolong life  
 1997 SREBP pathway elucidated  
 2006 PCSK9: Destroyer of LDL receptors

CHD, coronary heart disease; HMG CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LDL, low-density lipoproteins; PCSK9, proprotein convertase subtilisin/kexin type-9; SREBP, sterol regulatory element-binding protein.

than a “normal” aorta. Three years later, a Russian pathologist induced atherosclerosis in rabbits fed a high cholesterol diet. In 1919, an American clinician correlated electrocardiographic changes in patients suffering from angina caused by ASCVD.<sup>2</sup> Subsequently, familial hypercholesterolemia was diagnosed and the cholesterol synthesis pathway described. Over the last 50 years, the LDL receptor was discovered and pharmaceutical agents, the statins which inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, were approved and prescribed to treat patients with hyperlipidemia (Table 13.1). More recently, the transcription factor sterol regulatory element-binding protein-1 (SREBP-1) was identified as well as its complex interaction with intracellular and nuclear elements to regulate LDL.

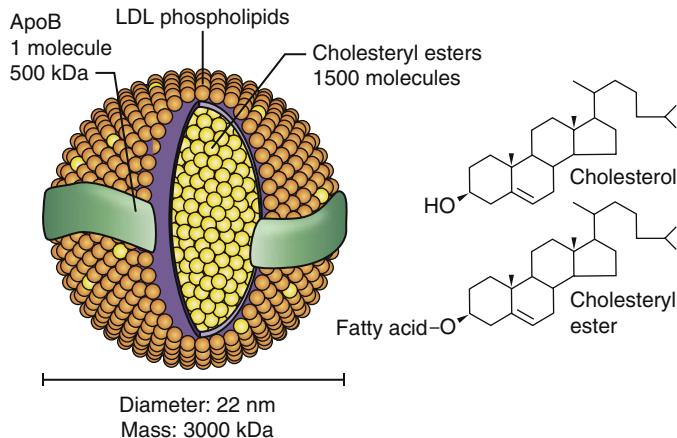
## PHYSIOLOGY AND METABOLISM OF LIPIDS

Lipids are hydrophobic and are chemically insoluble in blood. They are transported as lipoproteins in which the hydrophobic lipid components are surrounded by an envelope of hydrophilic phospholipids and proteins known as apolipoproteins (apo). This creates a water-soluble spherical particle that can be carried in the blood (Fig. 13.1). The principal function of lipoprotein particles is transporting lipids from the intestine and liver through the bloodstream to the cells of the body, where they can be stored, used for synthetic processes, and metabolized to yield energy. The various apolipoproteins, such as apo B, apo A, apo E, and apo C, serve as cofactors in metabolism of the contained lipid and as ligands to facilitate binding of lipoproteins to receptors on the surface of cells throughout the body. Five major lipoproteins are recognized.

**TABLE 13.1****Critical Historical Events that Led to the Discovery and Development of the Statins**

Year	Scientist(s)	Discovery
1913	Nikolai Anitschkow	Fed pure cholesterol to rabbits and demonstrated development of hypercholesterolemia and extensive aortic atherosclerosis
1950	John Gofman	Described the major classes of plasma lipoproteins using ultracentrifugation. Demonstrated direct and inverse association of LDL-C and HDL-C levels, respectively, with incidence of myocardial infarction
1964	Konrad Bloch and Feodor Lynen	Received Nobel Prize for unraveling the metabolic pathway of cholesterol synthesis
1972	Akira Endo	Discovered compactin, the forebearer to the first statin, from a blue-green mold
1973	Michael Brown and Joseph Goldstein	Received the Nobel Prize for the discovery of the LDL receptor and its feedback regulation

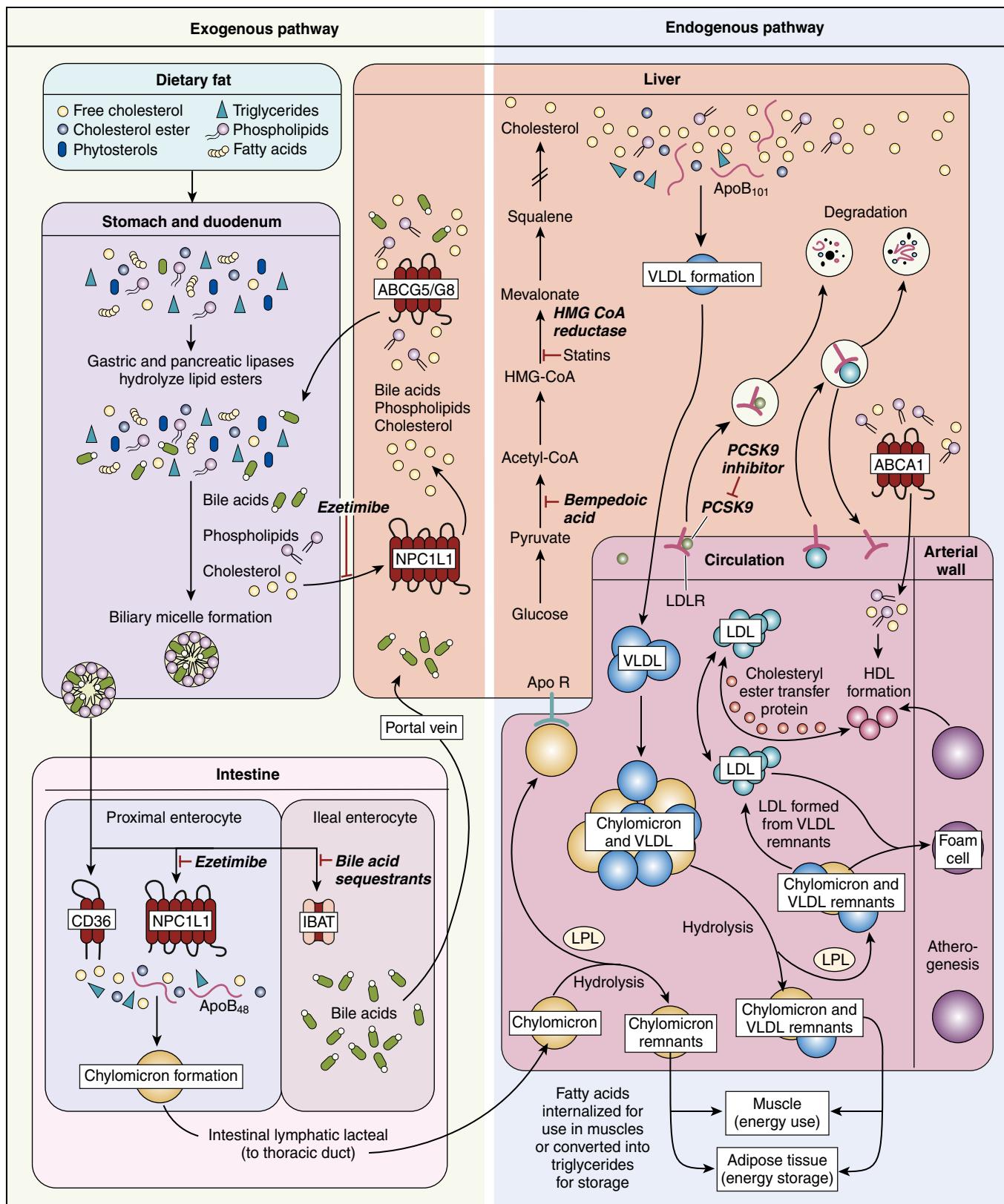
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.



**Figure 13.1** The Low-Density Lipoprotein (LDL) Molecule. ApoB, Apolipoprotein B. (From Goldstein JL, Brown MS. A century of cholesterol and coronaries: from plaques to genes to statins. *Cell*. 2015;161(1):161–172.)

## Chylomicrons

Lipoprotein metabolism can be divided into exogenous and endogenous phases. During the exogenous phase, both dietary lipids and recirculated lipids within bile are absorbed into enterocytes and packaged as very large lipoproteins called chylomicrons. Although dietary cholesterol and triglycerides are absorbed by different mechanisms within the gastrointestinal (GI) tract, they are combined in this single chylomicron particle for transport from the GI tract through the thoracic duct and into the circulation to the rest of the body. Triglycerides constitute approximately 90% of the chylomicron's lipid content. When present in significant concentration, chylomicrons account for the turbidity or “milkeness” of plasma, known as postprandial lipemia, which is seen in some individuals with metabolic and inherited disorders of lipid metabolism (Fig. 13.2). Chylomicrons



**Figure 13.2** Lipid Metabolism and Statins. HDL, high-density lipoprotein; LDL, low-density lipoprotein. (From Michos ED, McEvoy JW, Blumenthal RS. Lipid management for the prevention of atherosclerotic cardiovascular disease. *N Engl J Med*. 2019;381:1557–1567.)

**TABLE 13.2**

Adult Treatment Panel III Guidelines for the Evaluation of Fasting Lipid Profile

	Conventional Units (mg/dL)	SI Units (mmol/L)
<b>Low-Density Lipoprotein Cholesterol</b>		
Optimal	<100	<2.59
Near optimal	100–129	2.59–3.34
Borderline high	130–159	3.37–4.12
High	160–189	4.14–4.90
Very high	>190	>4.92
<b>High-Density Lipoprotein Cholesterol</b>		
Low	<40	<1.04
High	>60	>1.55
<b>Triglycerides</b>		
Normal	<150	<1.70
Borderline	150–199	1.70–2.25
High	200–499	2.26–5.64
Very high	>500	>5.65

SI, Standard international.

are distinguished by the presence of one apo B-48 molecule in each particle. In the bloodstream, the enzyme lipoprotein lipase (LPL) hydrolyzes the triglyceride contained within the chylomicron into free-fatty acids (FFAs). FFAs are taken up by peripheral tissues and used for energy. In adipose and muscle cells, FFAs can also be re-esterified into triglycerides and stored for future energy production. The remaining triglyceride-poor chylomicron remnant contains only the absorbed dietary cholesterol, which is then transported to the liver for storage. Although chylomicrons are typically considered a transport lipoprotein, evidence suggests atherosclerotic lesions contain apo B-48 within plaque, thus implicating these chylomicron remnants as atherogenic particles.<sup>7,8</sup>

### Very-Low-Density Lipoproteins

The endogenous phase of lipoprotein metabolism involves the hepatic formation of very-low-density lipoproteins (VLDLs) containing cholesterol and triglycerides derived from stores within the liver and adipocytes (Table 13.2). Each VLDL particle contains apo C and E as well as one molecule of apo B-100 per particle. Similar to chylomicrons, the predominant lipid component of VLDL is triglyceride, which accounts for approximately 70% of its lipid content. Although not as large as chylomicrons, VLDL is large enough to cause lipemia when present in very high concentrations. VLDL is released from the liver into the bloodstream, where LPL again facilitates removal of the triglyceride component of VLDL and presents it to the muscle cell as fuel for energy production. Through this endogenous mechanism, triglycerides stored in adipocytes, hepatocytes, and muscle cells can be used for energy during fasting or starvation as a more energy-rich alternative to glucose. As the triglyceride is removed, two additional atherogenic lipoprotein particles are formed: VLDL remnants and intermediate-density lipoproteins (IDLs).

### Intermediate Density Lipoprotein (Remnant Lipoprotein)

IDLs carry cholesterol esters and triglycerides. IDLs, similar to LDL, have been shown to increase the risk of cardiovascular disease. These triglyceride-rich lipoprotein particles are present in patients with metabolic syndrome and type 2 diabetes mellitus. The MARS study showed that IDL is associated with increased carotid artery intima-media thickness (CIMT).<sup>9</sup>

### Low-Density Lipoprotein

In addition to LPL, hepatic lipase participates in the conversion of IDL to LDL, the most atherogenic of all lipoprotein particles. Although a number of other apolipoproteins are attached to the original VLDL particle, only one, apo B-100, is present in each LDL particle (see Fig. 13.1). LDL binds to specific LDL receptors on the surface of each cell, facilitating transfer of the remaining cholesterol to these cells, where it can be stored and used as cell membranes, steroid hormones, and bile acids. The number of exposed LDL receptors is regulated by the intracellular concentration of cholesterol within each cell. When excess plasma LDL is present, atherosclerosis can possibly increase in proportion to the concentration of circulating LDL.

Nabel and Braunwald received the Nobel Prize in 1985 for discovering the LDL receptor.<sup>10,11</sup> They were able to demonstrate that the circulating LDL concentration in plasma is determined by the number of LDL receptors on the various cells of the body, with the liver accounting for more than 70% of this total receptor number.<sup>12</sup> When the intracellular cholesterol content of the cells is low, LDL receptor synthesis is upregulated, receptor numbers increase, and the LDL plasma concentration decreases. In contrast, when intracellular cholesterol is increased, LDL receptor synthesis is downregulated, receptor numbers diminish, and circulating LDL rises. Humans are born with a maximum number of LDL receptors and a very low circulating LDL level of 25 to 30 mg/dL (0.65 to 0.78 mmol/L).<sup>13</sup> Over a lifetime, the Western lifestyle of excessive calories, cholesterol, and saturated fat intake, along with inactivity, results in increasing intracellular cholesterol levels, causing secondary downregulation of LDL receptors. Therefore observed increases in excess plasma LDL-C levels coincide with the epidemic of atherosclerosis seen worldwide.

### High-Density Lipoproteins

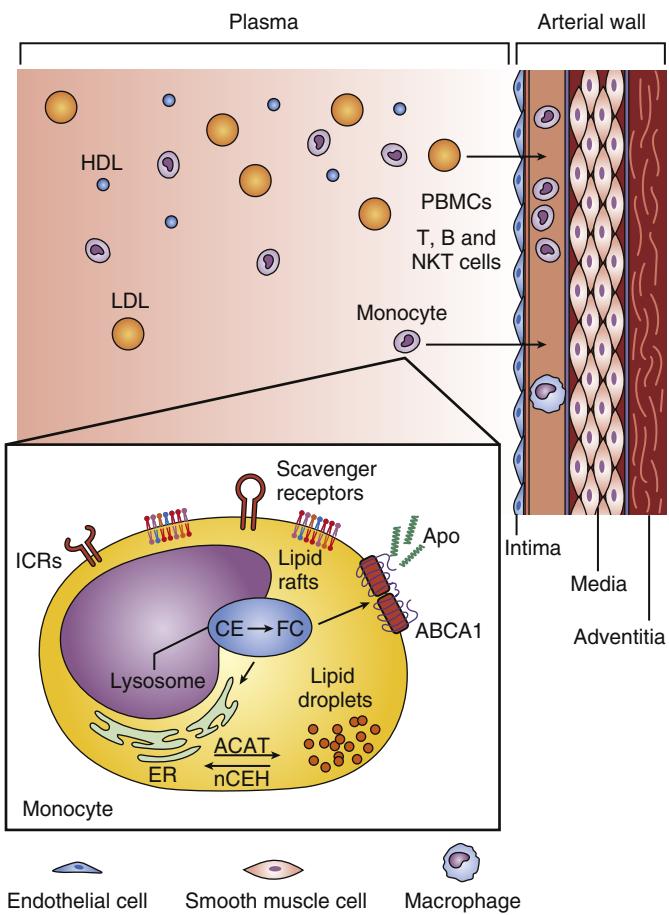
High-density lipoprotein (HDL) is synthesized by the liver and intestine as apo A-I, which is released into the bloodstream as a lipid-poor discoid particle. Stored cholesterol released from peripheral cells through the action of a specific transporter known as adenosine triphosphate-binding cassette (ABC) transporter A1 is absorbed by the discoid apo A-I and converted to cholesterol ester under the influence of lecithin-cholesterol acyltransferase (LCAT).<sup>14</sup> During this process,

HDL becomes a spherical particle. Additional cellular cholesterol is then added by another cassette transporter, ABCG1, and through the action of the scavenger receptor B1 (SR-B1). The HDL particle can then return to the liver, where it binds to hepatic SR-B1 and releases its cholesterol, or it can exchange a portion of its cholesterol content for triglyceride from VLDL through the chemical action of the cholesterol ester transfer protein (CETP). This removes triglyceride from VLDL, converting it into LDL, which is then removed from circulation through the hepatic LDL receptor. This process is known as “reverse cholesterol transport” and plays an important role in the antiatherogenic properties of the HDL particle.<sup>15,16</sup>

## PATHOPHYSIOLOGY OF ATHEROSCLEROSIS

Atherosclerosis is a pathologic process that begins in the arterial endothelial layer. Normal endothelium is smooth and repels circulating blood elements. On the other hand, damaged endothelium attracts various cellular elements. After the initiation of an atherogenic diet, patches of endothelial cells express selective adhesion molecules that bind to various classes of leucocytes.<sup>5</sup> Vascular cell adhesion molecule-1 (VCAM-1) binds to monocytes and T-lymphocytes detected in human atheromas.<sup>3</sup> In the setting of elevated LDL and low HDL, peripheral blood mononuclear cells become cholesterol enriched (Fig. 13.3). Intracellular droplets of cholesterol ester accumulate in these engorged cells, and give them a characteristic appearance, “foam cells.”<sup>17</sup> Foam cells are more apt to adhere to damaged endothelium and then migrate into the intima layer and become macrophages. In response to this, VSMC proliferate and cause thickening of the intima.<sup>6</sup> As the process is repeated, plaque thickness increases and a fibrous cap is formed (Fig. 13.4).<sup>18</sup> This pathologic process is the same in the peripheral and cerebrovascular circulation as it is in the coronary arteries. To varying degrees, the traditional risk factors are also similar, regardless of the location of atherosclerotic disease, including hyperlipidemia.<sup>19</sup>

The damaged endothelium also becomes permeable to LDL and other circulating atherogenic lipoproteins (VLDL remnants, IDL, and chylomicron remnants). Once inside the vessel wall, LDL is oxidized by free radicals, furthering the inflammatory immune response and initiating the pathologic process of atherosclerosis. Oxidized LDL is subsequently absorbed through specific scavenger receptors into fixed tissue macrophages, thereby transforming them into lipid-filled foam cells (Fig. 13.5). Groups of foam cells accumulate underneath the endothelium and become the initial lesion of atherosclerosis (the fatty streak).<sup>4</sup> As this process continues, the foam cells undergo apoptosis (programmed cell death) allowing the lipid contained in them to spill out to form the lipid core of an atherosclerotic plaque. The initial response of the arterial wall is to expand, a process known as positive remodeling. As the plaque increases in thickness, it begins to encroach on the arterial lumen, thereby reducing the blood flow to points distal.<sup>20</sup> The concept of stable and unstable plaque has been developed, with

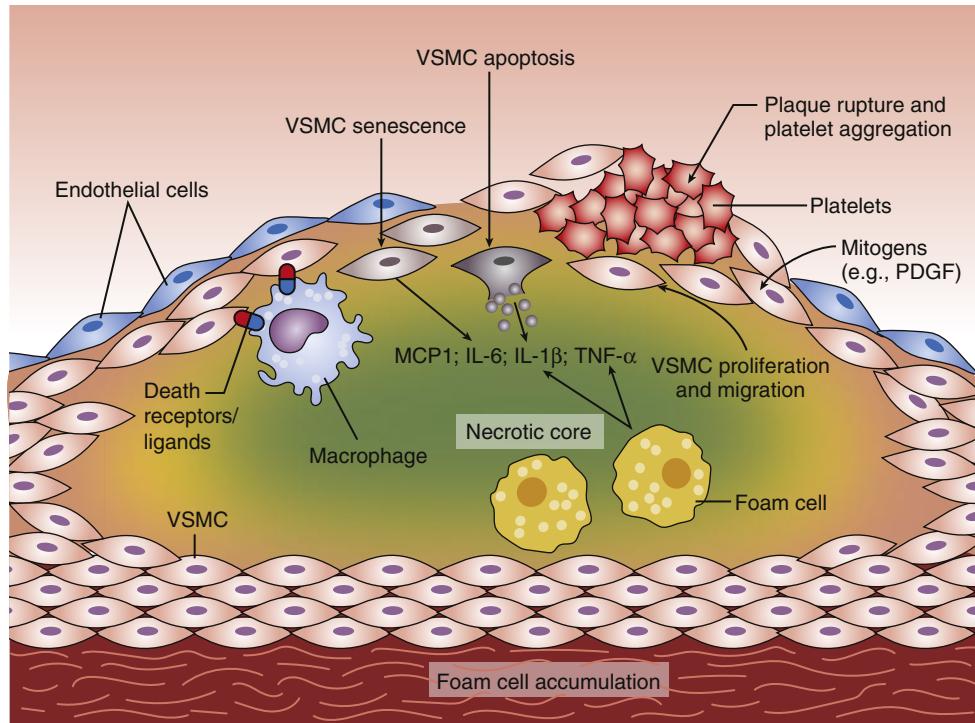


**Figure 13.3** Low-density lipoprotein and monocytes invade the endothelial layer. *Apo*, apolipoproteins; *ER*, extended-release; *HDL*, high-density lipoprotein; *LDL*, low-density lipoproteins. (From Sorci-Thomas MG, Thomas MJ. Microdomains, inflammation, and atherosclerosis. *Circ Res*. 2016;118(4):679–691.)

stable plaques possessing a thick fibrous cap and solid lipid core. Plaques accumulating a large lipid core trigger an intense local inflammatory reaction as this lipid is oxidized resulting in the infiltration of additional macrophages and inflammatory cells. The vulnerable or unstable plaque usually remains small and does not critically compromise the luminal diameter (Fig. 13.6). However, the thin fibrous cap is prone to ulceration or rupture. When this occurs, a platelet-rich clot rapidly forms on top of the plaque and produces complete obstruction of the involved artery and subsequent acute clinical infarction or ischemia. The relationship between LDL level, plaque formation and ASCVD has been extensively studied. At low physiologic LDL levels (20–40 mg/dL), the probability of LDL particle retention and atherosclerosis development is quite low. As LDL-C levels increase, there is a dose-dependent progressive formation of atherosclerotic plaque.<sup>21</sup>

## DIAGNOSIS OF ATHEROGENIC LIPID DISORDERS

The Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) recommended that all adults older than 20 years be screened for hyperlipidemia



**Figure 13.4** Interaction of cellular elements to form the lipid core and fibrous cap. (From Bennett MR, Sinha S, Owens GK. Vascular smooth muscle cells in atherosclerosis. *Circ Res*. 2016;118(4):692–702.)

every 5 years with a fasting lipoprotein profile.<sup>22,23</sup> Blood levels should include total cholesterol (TC), triglycerides, HDL cholesterol (HDL-C), and LDL-C. It is recommended that patients be in their usual state of health and fast for 12 hours before testing. Blood should be drawn after sitting comfortably for 5 minutes and with less than 1 minute of tourniquet time. If TC is greater than 200 mg/dL (5.18 mmol/L) or HDL is less than 40 mg/dL (1.04 mmol/L), a fasting lipoprotein profile should be obtained to better quantify the patient's atherosclerotic risk.

### Fasting Lipid Profile

ATP III recommended new guidelines for the evaluation of a fasting lipid profile (see Table 13.2). TC is not a good risk predictor because it can be increased by elevated HDL, which is usually a lower risk lipid profile, or decreased by low HDL, which is a higher risk lipid profile. The presence of very high triglyceride levels can also elevate TC and suggest a higher risk lipid profile than actually may be present.

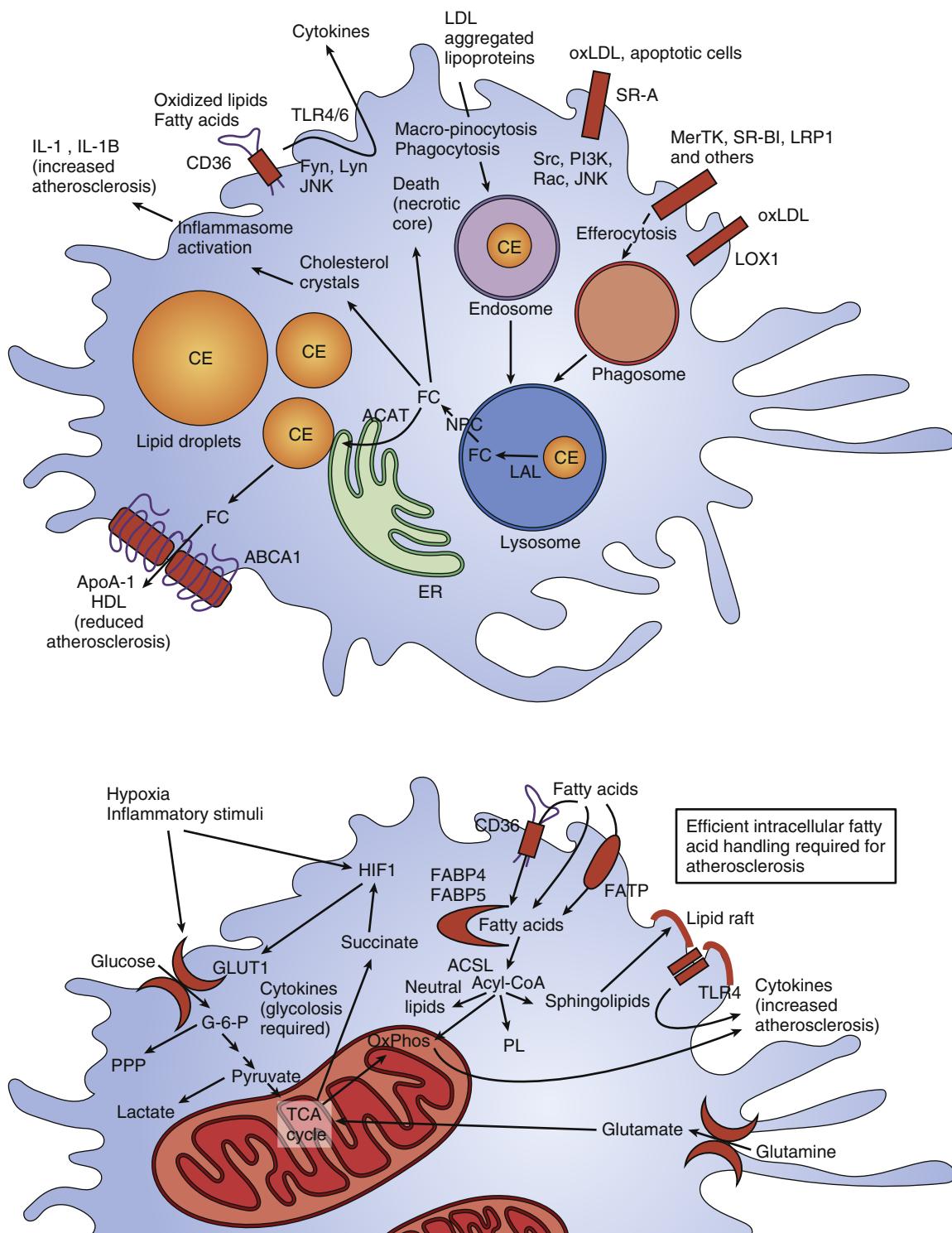
LDL-C has been shown to be the most predictive lipoprotein fraction for determining atherosclerosis risk in both epidemiologic and interventional studies, and the associated risk is directly proportional to the LDL-C concentration over a wide range of values.<sup>24,25</sup> HDL-C is equally predictive in epidemiologic studies, with an inverse relationship between the HDL-C concentration and risk for atherosclerosis. The risk associated with each of these lipoprotein fractions is additive in individuals with increased LDL-C and decreased HDL-C.<sup>26</sup> The role of elevated triglycerides in risk assessment is tougher to discern. When very sophisticated analyses of triglyceride-rich lipoproteins are performed, it is evident that large chylomicrons and VLDLs are not atherogenic, but the smaller remnant forms of

both these lipoproteins and the presence of IDL definitely confer increased atherogenicity.<sup>27</sup>

Clinically, elevated triglycerides in the presence of type 2 diabetes, metabolic syndrome, or familial combined dyslipidemia should indicate an increase in the risk for ASCVD. Very high levels of triglycerides (>1000 mg/dL [11.3 mmol/L]) are also associated with an increased risk for pancreatitis. Atherogenic dyslipidemia is a characteristic lipoprotein pattern frequently observed in patients with type 2 diabetes mellitus and the metabolic syndrome. In this condition, the LDL-C is often unimpressive or frankly low, but it is associated with elevated triglycerides with a decreased HDL-C concentration. More important, however, is the change in the number and composition of LDL particles associated with the metabolic syndrome and type 2 diabetes, rendering them more atherogenic. This LDL is described as “small, dense LDL,” which is an increased number of particles that contain less cholesterol per particle. Studies have shown that it is the number of LDL particles (LDL-P) that truly reflects the risk related to this profile.<sup>28</sup> LDL-P can be determined by lipid analysis using nuclear magnetic resonance (NMR) studies. Because each LDL-P contains one apo B-100 molecule, another method of more accurately assessing the risk conferred by an individual's LDL profile is to measure the apo B-100 level. Complete analysis may provide a better risk assessment because the individual risks associated with each lipoprotein abnormality in type 2 diabetes mellitus and metabolic syndrome are additive.

### Non-High-Density Lipoprotein Cholesterol in Risk Assessment

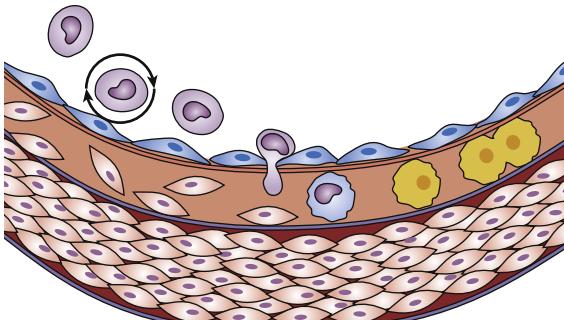
Non-HDL-C has been recognized in epidemiologic studies as one of the better predictors of atherosclerotic risk.<sup>29</sup> Non-HDL-C is easily calculated by subtracting HDL-C from TC.



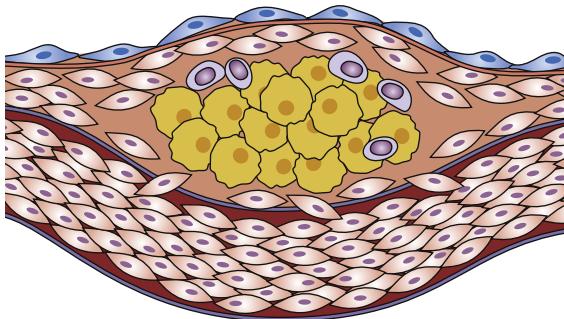
**Figure 13.5** Complex interaction of lipids and macrophages in atherosclerosis. *ApoA-I*, Apolipoproteins A-1; *ER*, endoplasmic reticulum; *HDL*, high-density lipoprotein; *LDL*, low-density lipoproteins. (From Tabas I, Bornfeldt KE. Macrophage phenotype and function in different stages of atherosclerosis. *Circ Res*. 2016;118(4):653–667.)

ATP III recommended the use of non-HDL-C (Box 13.2) as a way to more accurately assess risk in patients with increased triglycerides and made this a secondary target of therapy after the primary therapeutic goal for LDL-C is attained (vide infra). Non-HDL-C essentially represents the cholesterol

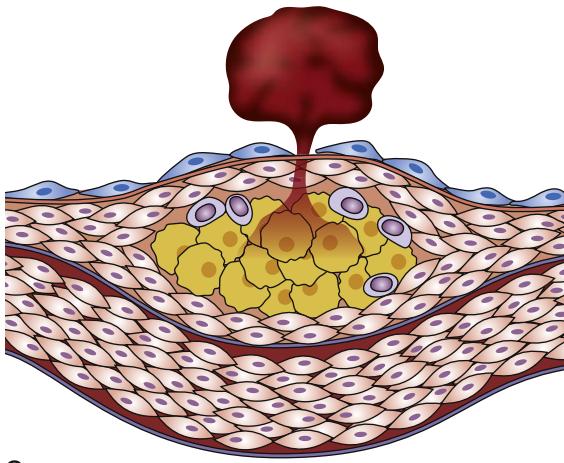
content in all of the apo B-containing atherogenic lipoproteins: non-HDL-C = LDL-C + IDL cholesterol + VLDL-C + lipoprotein-(a) (Lp[a]). However, these more specialized studies of cholesterol fractions are significantly more expensive than a routine lipid profile. Therefore it is recommended that the



A



B



C

**Figure 13.6** Initiation of plaque: the stable versus vulnerable plaque. (A) Recruitment of leucocytes in a developing plaque. (B) T-lymphocytes and macrophages in the intima and plaque formation. (C) Plaque rupture and thrombus formation, may lead to vessel occlusion. (From Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation*. 2002;105(9):1135–1143.)

initial risk evaluation and lipid management be performed with the standard LDL-C, HDL-C, and non-HDL-C measurements and that specialized testing be reserved for unusual situations or for fine tuning of therapy.

### Lipoprotein(a)

Epidemiologic studies have established that Lp(a) is associated with increased atherosclerotic risk and risk of cardiovascular events, particularly ischemic stroke.<sup>30,31</sup> However, little is known about the metabolism of this hybrid lipoprotein

### BOX 13.2

#### Importance of Non-High-Density Lipoprotein Cholesterol

- Known predictor of CHD in epidemiology
  - Equivalent to total apo B-100 and TC/HDL
  - Represents the sum of LDL, Lp(a), IDL, and VLDL: all atherogenic apo B-containing lipoproteins
  - Lipid equivalent of hemoglobin A<sub>1c</sub>
- Non-HDL cholesterol = TC – HDL cholesterol.

CHD, coronary heart disease; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; Lp(a), lipoprotein (a); TC, total cholesterol; VLDL, very low-density lipoprotein.

particle. There is a lack of interventional data to establish Lp(a) as a legitimate modifiable atherosclerotic risk factor, and there are few effective therapies for lowering levels of this lipoprotein. The European Atherosclerosis Society recommends checking Lp(a) levels in patients at moderate or high risk of cardiovascular disease, including patients with a personal or family history of premature atherosclerosis, familial hypercholesterolemia, family history of elevated Lp(a), recurrent atherosclerotic events despite statin therapy and meeting accepted goals for therapy, and patients with increased 10-year risk for major cardiovascular events according to European or U.S. guidelines.<sup>31</sup>

## EVOLUTION OF THE GUIDELINES FOR MANAGEMENT AND THERAPEUTIC GOALS FOR LIPOPROTEIN DISORDERS

### Adult Treatment Panel I

The NCEP was launched in 1988. It has served as the driving force for lipid management guidelines since the publication of the ATP I report and recommendations for standardization of clinical measurement of lipids.<sup>32</sup> ATP I sought to educate the U.S. population regarding coronary heart disease (CHD) risk and to encourage cholesterol reduction. The focus of ATP I was education and lifestyle intervention. Interventional therapy was reserved for individuals at increased risk, including those with an LDL greater than 190 mg/dL (4.92 mmol/L) or those with an LDL-C greater than 160 mg/dL (4.14 mmol/L) and two or more additional CHD risk factors (Box 13.3).

### Adult Treatment Panel II

The NCEP published the ATP II report in 1993 after the introduction of HMG-CoA reductase inhibitors (statins).<sup>23</sup> The NCEP guidelines adopted the ATP I recommendations and added secondary prevention of CHD in patients with known CAD. Several small trials verified the benefit of modifying diet and using statins. Lowering LDL-C was the main goal; however, significant increases in HDL-C were observed, and this lipid change was thought to contribute to the positive outcomes of these surrogate endpoint trials. On the basis of these secondary

**BOX 13.3****Risk Factors for Coronary Heart Disease in Addition to Low-Density Lipoprotein Cholesterol**

- Cigarette smoking
- Hypertension ( $>140/90$  mm Hg)
- Low HDL cholesterol ( $<40$  mg/dL) ( $1.04$  mmol/L)
- Family history:
  - CHD in male first-degree relative younger than 55 years
  - CHD in female first-degree relative younger than 65 years
- Age (men older than 45 years, women older than 55 years)

*CHD*, coronary heart disease; *HDL*, high-density lipoprotein.

prevention studies, ATP II recommended that patients with known CHD have the more aggressive therapeutic goal for LDL-C of 100 mg/dL or less.<sup>33</sup>

Another observation made in these trials was that coronary events were frequent in patients with coronary stenosis less than 70%. This introduced the concept of a “vulnerable plaque.”<sup>34</sup> This is a small plaque with a large lipid core and a thin fibrous cap, with less than critical stenosis but a potential for inducing intraluminal thrombosis. It was suggested that statin therapy “stabilized” this plaque by helping prevent rupture or ulceration of the fibrous cap.

On the basis of these secondary prevention studies, ATP II recommended that patients with known CHD have the more aggressive therapeutic goal for LDL-C of 100 mg/dL or less.

### Adult Treatment Panel III

Initially published as an executive summary and later as a full report in 2002, ATP III was the first evidence-based report from the NCEP that focused on large clinical trial data.<sup>22</sup> Four large trials examined primary and secondary prevention strategies.<sup>35–38</sup> As a result, ATP III recommended a more aggressive approach to risk assessment and management of lipid levels. Table 13.2 shows the new classification recommended by ATP III for LDL-C, HDL-C, and triglyceride levels in the initial risk assessment of individuals based on lipid levels. ATP III also recommended more aggressive goals of therapy for lipid management in patients with both established CHD and CHD risk equivalents. In addition to continuing the evaluation of additional risk factors (see Box 13.3) recommended by ATP I and II, ATP III added an emphasis on 10-year risk assessment for CHD by using the Framingham risk assessment algorithm.<sup>39</sup>

### Coronary Heart Disease Risk Equivalents

Another feature of ATP III was the designation of three conditions as “CHD risk equivalents,” in that each carried a 10-year risk for a major coronary event that was equal to that of patients with established CHD (>20% per 10 years). Diabetes mellitus, other atherosclerotic diseases including PAD, carotid artery disease, and abdominal aortic aneurysm, and the presence of multiple cardiovascular risk factors that conferred a 10-year risk of greater than 20%, as judged by the Framingham risk assessment tool, received the designation of “CHD

**BOX 13.4****Coronary Heart Disease Risk Equivalents**

- Other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease)
- Diabetes
- Multiple risk factors that confer a 10-year risk for coronary heart disease greater than 20%

**TABLE 13.3**

Comparison of Low-Density Lipoproteins Cholesterol and Non-High-Density Lipoprotein Cholesterol Therapeutic Goals by Categories of Risk

Risk Category	LDL CHOLESTEROL GOAL		NON-HDL CHOLESTEROL GOAL	
	(mg/dL)	(mmol/L)	(mg/dL)	(mmol/L)
CHD and CHD risk equivalent (10-year risk for CHD >20%)	<100	<2.59	<130	<3.37
Multiple (2+) risk factors and 10-year risk <20%	<130	<3.37	<160	<4.14
0–1 Risk factor	<160	<4.14	<190	<4.92

*CHD*, coronary heart disease; *LDL*, low-density lipoprotein; *non-HDL*, non-high-density lipoprotein.

risk equivalent” (Box 13.4). Although discussed in the ATP II report, ATP III was the first formal recognition of the importance of PAD as a significant indicator of CHD.

### Risk Stratification

ATP III suggested patients be categorized into one of three risk strata and that aggressiveness matched therapeutics to the assessed risk level. These three categories are as follows: (1) high risk – established CHD and CHD risk equivalents; (2) intermediate risk – multiple (2+) risk factors; and (3) low risk – 0 to 1 risk factor. In addition to the goals recommended for LDL-C, in individuals with triglyceride levels greater than 200 mg/dL, a secondary goal was recommended for management of non-HDL-C (discussed previously). Table 13.3 shows the LDL and non-HDL-C goals for the treatment of individuals in each of these three risk categories. Although ATP III introduced the issue of basing lipid management on an individual’s 10-year risk assessment, management of individuals with very high LDL levels or severe individual risk factors that conferred a high lifetime risk was continued as recommended by ATP I and II. In 2013, the ACC/AHA published a heart risk calculator that incorporated the following elements: age, sex, race, total cholesterol, HDL, systolic and diastolic pressures, whether the patient was treated with antihypertensives, diabetic or actively smoking. The tool gives out a 10-year risk of ASCVD.

**TABLE 13.4**

Adult Treatment Panel III Low-Density Lipoproteins Cholesterol and Non-High-Density Lipoprotein Cholesterol Therapeutic Goals by Risk Category

Risk Category	LDL CHOLESTEROL		NON-HDL CHOLESTEROL	
	(mg/dL)	(mmol/L)	(mg/dL)	(mmol/L)
CHD or equivalent (10-year risk >20%)	<100	<2.59	<130	<3.37
≥2 Risk factors (10-year risk ≤20%)	<130	<3.37	<160	<4.14
Very high risk (optional)	<70	<1.81	<100	<2.59

CHD, coronary heart disease; LDL, low-density lipoprotein; non-HDL, non-high-density lipoprotein.

Modified from National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106:3143–3421.

### The 2013 ACC/AHA Guidelines

After ATP III was published, trials of very aggressive lipid lowering in very high-risk individuals were conducted, and the LDL-C levels reached were considerably lower than those recommended by ATP III.<sup>40,41</sup> The positive clinical outcomes of these aggressive lipid-lowering trials resulted in an addendum to the ATP III report published in 2004 that recommended lower therapeutic goals for LDL-C and non-HDL-C in patients with very high-risk CHD (Table 13.4).<sup>42</sup> In 2005, the ACC/AHA published guidelines specifically directed to the management of patients with PAD. Patients with established PAD should be treated with statins to achieve a target LDL of less than 100 mg/dL (class I recommendation). Treatment goals of less than 70 mg/dL are reasonable in patients with lower extremity PAD who are at high risk for events (class IIa recommendation).<sup>19</sup>

The 2013 guidelines from the ACC/AHA<sup>43</sup> reaffirmed the more aggressive therapeutic goals for LDL-C and non-HDL-C and recommended targeting 4 statin benefit groups: individuals with clinical ASCVD, those with LDL >190 mg/dL, diabetics and non-diabetics between 40 and 75 years, and LDL in the 70 to 189 mg/dL and ASCVD risk >7.5%.

### The 2018 ACC/AHA Guidelines

Several RCTs were published after the 2013 guidelines appeared in print prompting another look at existing recommendations. Completed trials showed the benefit of PCSK9 inhibitors and ezetimibe in reducing ASCVD risk but not niacin and cholesterol-ester transfer protein inhibitors. The updated guidelines contained both broad and tailored

recommendations, according to the individual patient's risk factors and LDL-C level. An emphasis on adopting a heart-healthy lifestyle for everyone, prevention of ASCVD in patients 40–75 years of age, and shared decision-making between clinician and patient before considering the start of a statin, are all examples of broad recommendations. The guidelines recommended driving the LDL-C level to 70 mg/dL or less in very high-risk patients with ASCVD. Patients with severe primary hypercholesterolemia (LDL-C >190 mg/dL) should be on a high intensity statin therapy, regardless of risk. Moreover, in diabetics between 40 and 75 years of age, moderate intensity statin should be initiated for LDL-C >70 mg/dL.<sup>44</sup>

## CLINICAL TRIALS OF THE MANAGEMENT OF DYSLIPIDEMIA IN PERIPHERAL ARTERIAL DISEASE

Most clinical trials were designed to test the efficacy of statins and the benefit of driving down LDL levels in reducing cardiovascular mortality. The secondary benefit of improving PAD was realized post hoc. Patients with PAD generally receive less intensive risk factor modification than do patients with coronary disease, although they share similar vascular risk profiles.<sup>45</sup> As few as a third of patients with PAD receive statin therapy. The Heart Protection Study (HPS) data are provocative (see the next section); they indicate that aggressive lipid management produces a definite reduction of approximately one-sixth in the risk for peripheral vascular events not only in patients with preexisting PAD but also in high-risk individuals without previously diagnosed PAD. This finding highlights the need for further clinical trials that have prevention of peripheral vascular disease as their primary endpoint. These additional trials should also include patients with early forms of PAD.

### Early Trials Linking Lipid Therapy to Atherosclerosis

The Program on the Surgical Control of the Hyperlipidemias (POSCH) and the Cholesterol Lowering Atherosclerosis Study (CLAS) established the basis for future studies examining dyslipidemia.<sup>46,47</sup> Both studies used angiographic evidence to support the conclusion that lipid therapy is effective in controlling the progression of atherosclerosis.

POSCH used ileal bypass surgery to lower lipid levels and demonstrated a reduction in the progression of atherosclerosis. At the formal closure of the POSCH trial, no significant difference was noted between the control and active therapy groups in the progression of PAD. However, all participants were observed for an additional 5 years after the trial ended. At the 5-year follow-up evaluation, an ankle-brachial index (ABI) of less than 0.95 was present in 41 of 120 control patients and in 24 of 126 ileal bypass patients, thus conferring a 44% risk reduction for development of an abnormal ABI. Furthermore, the risk of development of clinical manifestations of PAD was reduced by 30%.<sup>48</sup>

Anatomic assessment of the effect of lipid-lowering therapy was also evaluated in the CLAS trial.<sup>49</sup> One hundred and sixty-two nonsmoking men between the ages of 40 and 59 years who had previously undergone coronary artery bypass graft surgery were randomized to a combination of colestipol, niacin, and diet, or to placebo and diet. Coronary angiography after 2 years demonstrated a significant reduction in the progression of atherosclerosis in the group that received therapy with colestipol plus niacin.

## NONPHARMACOLOGIC THERAPY FOR DYSLIPIDEMIA

ATP III issued evidence-based guidelines on cholesterol management.<sup>42</sup> Therapeutic lifestyle change (TLC) was recommended as an essential modality in the clinical management of hypercholesterolemia. The ATP III report recommends initiation of TLC based on the LDL goal stratified by risk category (Table 13.5). Any person at high risk or moderately high risk who has lifestyle-related risk factors is a candidate for TLC to modify these risk factors, regardless of LDL-C level.

## Dietary Changes

Individuals at low risk should initiate TLC at an LDL-C level of greater than 160 mg/dL (4.14 mmol/L); those with two or more risk factors and a Framingham 10-year CHD risk assessment of less than 10% should initiate TLC at an LDL-C level of greater than 130 mg/dL (3.37 mmol/L); and individuals with two or more risk factors and a 10-year CHD risk assessment of 10% to 20% should initiate TLC at an LDL-C level of 130 mg/dL (3.37 mmol/L). Finally, any high-risk patient with CHD or a CHD risk equivalent and a 10-year CHD risk assessment of greater than 20% should initiate TLC at an LDL-C level of greater than 100 mg/dL (2.59 mmol/L).

A plant-based diet that eschews any animal source of food is ideal for lowering TC. Dietary modifications include high amounts of fruits and vegetables, legumes, and whole grains as part of a low-fat diet. These modifications have been shown to reduce LDL and TC.<sup>50</sup> ATP III recommends a reduction in saturated fats to less than 7% of total calories and cholesterol to less than 200 mg/day. The addition of other dietary products

TABLE 13.5

**ATP III Low-Density Lipoproteins Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Change and Drug Therapy in Different Risk Categories and Proposed Modifications Based on Recent Clinical Trial Evidence**

Risk Category	LDL Cholesterol Goal	Initiate TLC	Consider Drug Therapy <sup>a</sup>
High risk: CHD <sup>b</sup> or CHD risk equivalents <sup>c</sup> (10-year risk >20%)	<100 mg/dL (2.59 mmol/L) (optional goal: <70 mg/dL [1.81 mmol/L]) <sup>d</sup>	≥100 mg/dL (2.59 mmol/L) <sup>e</sup>	≥100 mg/dL (2.59 mmol/L) <sup>f</sup> (if <100 mg/dL, consider drug options) <sup>a</sup>
Moderately high risk: 2+ risk factors <sup>g</sup> (10-year risk of 10%–20%) <sup>h</sup>	<130 mg/dL (3.37 mmol/L) <sup>i</sup>	≥130 mg/dL (3.37 mmol/L) <sup>j</sup>	≥130 mg/dL (3.37 mmol/L) (if 100–129 mg/dL [2.59–3.34 mmol/L], consider drug options) <sup>j</sup>
Moderate risk: 2+ risk factors <sup>g</sup> (10-year risk <10%) <sup>h</sup>	<130 mg/dL (3.37 mmol/L)	≥130 mg/dL (3.37 mmol/L)	≥160 mg/dL (4.14 mmol/L)
Lower risk: 0–1 risk factor <sup>k</sup>	<160 mg/dL (4.14 mmol/L)	≥160 mg/dL (4.14 mmol/L)	≥190 mg/dL (4.92 mmol/L) (if 160–190 mg/dL [4.14–4.92 mmol/L], LDL-lowering drug optional)

<sup>a</sup>When LDL-lowering drug therapy is used, it is advised that the intensity of therapy be sufficient to achieve at least a 30%–40% reduction in LDL cholesterol levels.

<sup>b</sup>CHD included a history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia.

<sup>c</sup>CHD risk equivalents include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [transient ischemic attacks, stroke of carotid origin, or >50% obstruction of a carotid artery]), diabetes, and 2+ risk factors with a 10-year risk for hard CHD >20%.

<sup>d</sup>Very high risk favors the optional LD cholesterol goal of <70 mg/dL (1.81 mmol/L) and, in patients with high triglyceride levels, non-HDL cholesterol <100 mg/dL (2.59 mmol/L).

<sup>e</sup>Any person at high risk or moderately high risk who has lifestyle-related risk factors (e.g., obesity, physical inactivity, elevated triglycerides, low HDL cholesterol, or metabolic syndrome) is a candidate for TLCs to modify these risk factors regardless of LDL cholesterol level.

<sup>f</sup>If baseline LDL cholesterol is <100 mg/dL (2.59 mmol/L), institution of an LDL-lowering drug is a therapeutic option on the basis of available clinical trial results. If a high-risk person has high triglyceride levels or low HDL cholesterol, combining a fibrate or nicotinic acid with an LDL-lowering drug can be considered.

<sup>g</sup>Risk factors include cigarette smoking, hypertension (blood pressure ≥140/90 mm Hg or taking antihypertensive medication), low HDL cholesterol (<40 mg/dL [1.04 mmol/L]), family history of premature CHD (CHD in male first-degree relative <55 years of age, CHD in female first-degree relative <65 years of age), and age (men ≥45 years; women ≥65 years).

<sup>h</sup>Electronic 10-year risk calculators are available at <https://www.nhlbi.nih.gov/health-topics/blood-cholesterol>.

<sup>i</sup>Optional LDL cholesterol goal, <100 mg/dL (2.59 mmol/L).

<sup>j</sup>For moderately high-risk persons, when the LDL cholesterol level is 100–129 mg/dL (2.59–3.34 mmol/L) at baseline with lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL cholesterol level of <100 mg/dL (2.59 mmol/L) is a therapeutic option on the basis of available clinical trial results.

<sup>k</sup>Almost all people with zero or one risk factor have a 10-year risk of <10%, and 10-year risk assessment in people with zero or one risk factor is thus not necessary.

ATP III, Adult Treatment Panel III; CHD, coronary heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TLC, therapeutic lifestyle change.

From Grundy SM, Cleeman JL, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation*. 2004;110:227–239.

**TABLE 13.6****Essential Components of Therapeutic Life-style Changes**

Component	Recommendation
<b>LDL-Raising Nutrients</b>	
Saturated fats <sup>a</sup>	<7% of total calories
<b>Therapeutic Options for LDL Lowering</b>	
Plant stanols/sterols	2 g/day
Increased viscous (soluble) fiber	10–25 g/day
Total calories (energy)	Adjust total caloric intake to maintain desirable body weight/prevent weight gain
Physical activity	Include enough moderate exercise to expend at least 200 kcal/day

<sup>a</sup>Trans fatty acids are another LDL-raising fat that should be kept at low intake. LDL, low-density lipoprotein.

From National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106:3143–3421.

containing plant sterols or stanols, which are available on the shelves of most grocery stores, has been shown to reduce TC and LDL-C by 10% to 15%.<sup>51</sup> On the other hand, the consumption of trans-fatty acids is harmful because they increase TC and lower HDL-C. In a meta-analysis, increasing trans-fatty acids intake by 2% increased the incidence of CAD by 23%. Soluble fiber supplements are also suggested as adjuncts to dietary therapy. ATP III outlines maximal dietary therapy, including balancing energy intake and expenditure to maintain desirable body weight and prevent weight gain, which together can reduce LDL-C by 25% to 30% (Table 13.6). The PRE-DIMED study in Spain enrolled 7447 with increased CVD risk and demonstrated that a Mediterranean diet supplemented with olive oil or nuts decreased the incidence of major cardiovascular events.<sup>52</sup> A meta-analysis of gastric bypass studies showed an improved lipid profile in a majority of patients.<sup>53</sup>

## Exercise

At least moderate daily physical activity, to expend approximately 200 kcal/day is recommended. Physical activity has been reported to lower LDL and triglyceride levels, raise HDL-C, and improve insulin sensitivity. Inactivity impairs cardiovascular fitness and coronary blood flow. These effects can be readily reversed by regular activity. Physical activity in accord with a patient's overall health status should be encouraged. Additional benefits may be realized in the management of metabolic syndrome. Exercise specialists in addition to nutrition and diet professionals may be able to assist patients in achieving TLC (see Table 13.6). The ACC/AHA goals for exercise include 30 to 60 minutes of moderate physical activity 5 to 7

days a week in addition to increased activity in daily lifestyle activities.<sup>54,55</sup>

## PHARMACOLOGIC THERAPY FOR DYSLIPIDEMIA

Currently, the cornerstone of pharmacologic lipid management is the use of statins. Statin therapy can be in three forms: high, moderate or low intensity. Furthermore, there are other agents that are recommended for use, either in addition to or instead of a statin, when the latter is not tolerated or ineffective in achieving the desired LDL-C level. The major lipid lowering agents currently available, their mechanism of action, as well as novel agents are presented herein.

### Statins

The HMG-CoA reductase inhibitors (statins) are the most effective class of drugs for treating elevated LDL-C levels. This class of drugs has been shown to reduce LDL-C by 18% to 60%, raise HDL-C by 5% to 20%, and decrease triglycerides by 7% to 30%. Statins have been proven to reduce the risk of CHD, stroke, and PAD, as well as improve mortality. They have also proved to be safe, with very low occurrences of major adverse events. The reduction in LDL-C is dose-dependent and log-linear. The starting dose of each statin produces 75% to 80% of the maximal reduction in LDL-C, and with each subsequent doubling of the dose, an additional 6% reduction is typically achieved.

Statin therapy has been demonstrated to be safe and effective in lipid management. Transient elevation of transaminase level occurs infrequently and is usually self-limiting. Minor musculoskeletal side effects (myalgia without CPK elevation) have been reported in clinical practice but not detected in randomized trials. Rhabdomyolysis is rare (4 in 10,000) and if strongly suspected, warrants measurement of total creatine phosphokinase, and if significantly elevated (>10× the upper limit of normal), discontinuation of the medication (Table 13.7). Excess risk of myopathy with the 80-mg dose of simvastatin was identified in the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial, especially in the first 12 months of use.<sup>56</sup> This led the Food and Drug Administration (FDA) to recommend safety label changes, with recommendations regarding the prescription of the 80-mg dose of simvastatin, as well as adjusting the list of drugs to which the use of simvastatin is contraindicated.

Statin therapy is associated with an increased risk of new onset diabetes, and appears to be dose-dependent, with higher incidence in patients receiving high doses. In randomized trials, there was no evidence of a causal relationship between statins and malignancy or cognitive dysfunction.<sup>1,57</sup>

Statin therapy has also proved to be effective in improving pain-free walking time in patients with intermittent claudication.<sup>58,59</sup> In a multicenter randomized controlled trial of 354 people with claudication attributable to PAD, patients were randomized to placebo or to 10- or 80-mg doses of atorvastatin.

**TABLE 13.7**
**Summary of 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors**

<b>Available Drugs</b>	Lovastatin, Pravastatin, Simvastatin, Fluvastin, Atorvastatin, Rosuvastatin
<b>Lipid/lipoprotein</b>	LDL cholesterol: decrease of 18%–60%
<b>Effects</b>	HDL cholesterol: increase of 5%–25%
	Triglycerides: decrease of 7%–30%
<b>Major use</b>	To lower LDL cholesterol
<b>Contraindications</b>	
Absolute	Active or chronic liver disease
Relative	Concomitant use of cyclosporine, macrolide antibiotics, various antifungal agents, and cytochrome P-450 inhibitors (fibrates and nicotinic acid) should be undertaken with appropriate caution
Efficacy	Reduce risk for CHD and stroke
Safety	Side effects minimal in clinical trials
Major side/adverse effects	Myopathy, increased liver transaminases
<b>Usual Starting Dose</b>	
Lovastatin: 20 mg	Lovastatin: 80 mg
Pravastatin: 20 mg	Pravastatin: 80 mg
Simvastatin: 20 mg	Simvastatin: 40 mg <sup>a</sup>
Fluvastatin: 20 mg	Fluvastatin: 80 mg
Atorvastatin: 10 mg	Atorvastatin: 80 mg
Rosuvastatin: 5 mg	Rosuvastatin: 40 mg
Pitavastatin: 2 mg	Pitavastatin: 4 mg
Available dosing	Lovastatin: 10-, 20-, 40-mg tablets Pravastatin: 10-, 20-, 40-mg tablets Simvastatin: 5-, 10-, 20-, 40-, 80-mg tablets Fluvastatin: 20-, 40-mg capsules; 80-mg XL tablets Atorvastatin: 10-, 20-, 40-, 80-mg tablets Rosuvastatin: 5-, 10-, 20-, 40-mg tablets Pitavastatin: 1-, 2-, 4-mg tablets

<sup>a</sup>Patients already on the 80-mg dose for more than 12 months may continue at this dose. New patients started on simvastatin should not exceed 40 mg daily. CHD, coronary heart disease; FDA, Food and Drug Administration; HDL, high-density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LDL, low-density lipoprotein.

There was an improvement in pain-free walking in 63% of patients and significant change in ABI.<sup>60</sup>

The Scandinavian Simvastatin Survival Study (4S) was the first trial of lipid-lowering therapy in patients with established CHD to show a decrease in all-cause mortality and a reduction in CHD mortality and morbidity with statins compared with placebo. Patients exhibited a 30% reduction in CHD mortality and a 42% reduction in the incidence of nonfatal coronary events, with both outcomes being directly proportional to the reduction in LDL-C and TC levels. In addition, new or

worsening intermittent claudication symptoms were reduced by 38% in patients who received statin therapy versus those given placebo in 4S.<sup>61</sup>

The HPS, a trial of simvastatin, 40 mg/day, versus antioxidant vitamins or placebo in 20,536 participants at high risk for a CHD event, demonstrated an overall 19.8% risk for a first major vascular event on statin treatment compared with a 25.2% risk in the placebo group (a 24% relative risk reduction).<sup>40</sup> The average LDL-C difference between the two groups was 39 mg/dL (1.01 mmol/L) during a mean follow-up of 5 years. The event reduction was due mainly to a 20% reduction in noncoronary revascularization, including a decrease in the number of carotid endarterectomies. The HPS was also the most comprehensive evaluation of the effects of cholesterol-lowering therapy on major vascular events in patients with PAD. More than 6000 patients with PAD were included in this study. Risk reduction benefits were similar between PAD patients and CHD patients, and were reported in a separate subset analysis.<sup>62</sup> The HPS included more than 5900 diabetics who experienced similar benefits in clinical outcomes as nondiabetics. HPS was a landmark trial in the treatment of patients with PAD, given the large number of participants with preexisting disease. The results of HPS support the treatment of all patients with PAD with a statin agent for lipid-lowering therapy.

The high-risk elderly population was examined in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study.<sup>63</sup> A total of 5800 patients, ages 70 to 82 years, with a history of preexisting vascular disease (coronary, cerebral, or peripheral), or at increased risk for such disease because of smoking, hypertension, or diabetes, were randomized to 40 mg/day of pravastatin or placebo. Treated patients had a 34% reduction in their LDL-C level and a reduction in the rate of major coronary events by 19% and CHD mortality by 24%. The authors concluded that the study results allowed statin therapy to be safely extended to older persons.

The Treating to New Targets (TNT) study examined the safety and efficacy of aggressive LDL lowering. More than 10,000 patients with established CHD and LDL less than 130 mg/dL were randomized to atorvastatin either 10 or 80 mg daily. After nearly 5 years of follow-up, LDL levels were substantially lower in the patients treated with 80 mg daily (77 mg/dL) compared with patients taking atorvastatin 10 mg daily (101 mg/dL;  $P < 0.001$ ). In addition, major cardiovascular events were 22% lower in the patients taking atorvastatin 80 mg (8.7%) versus 10 mg (10.9%) ( $P < 0.001$ ).<sup>64</sup>

The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial enrolled 17,802 apparently healthy people with LDL levels less than 130 mg/dL and hs-CRP levels equal to or more than 2.0 mg/L to rosuvastatin or placebo. The trial was terminated early after a median 1.9 years of follow-up. Rosuvastatin reduced LDL-C by 50%; hs-CRP was decreased by 37%. The primary endpoint of major cardiovascular events or cardiovascular death decreased from 1.36 per 100 person-years with placebo to 0.77 per 100 person-years with rosuvastatin ( $P < 0.00001$ ).<sup>65</sup>

## Niacin

Niacin (nicotinic acid) was the first pharmacologic agent demonstrated to reduce cholesterol in clinical trials. It favorably affects all lipids and lipoproteins, with 15% to 35% increases in HDL-C and 5% to 25% decreases in LDL-C. Niacin inhibits lipoprotein synthesis, improves the clearance of triglyceride-rich lipoproteins from the circulation, and is also the most effective agent for raising HDL-C levels.

Adverse events are more common with niacin than with other lipid-lowering agents, and regular evaluation of liver function, glucose, and uric acid is indicated. Aspirin 30 minutes before niacin administration helps prevent flushing.<sup>66</sup> In addition, extended-release (ER) and enteric-coated ER niacin in which the frequency and intensity of flushing is reduced are available. Niacin is available over the counter, although over-the-counter forms of delayed-release or long-acting niacin should not be used because of a significant increase in hepatotoxicity.

Niacin is typically poorly tolerated at higher doses and is often used in combination with statins or other pharmacologic agents. The initial dosage should be 500 mg ER niacin by mouth nightly for 4 weeks and then increased by 500 mg/day every 4 weeks based on effect and tolerance. The maximum dose is 2 g/day ER niacin. Data from the Comparative Effects on Lipid Levels of Niaspan and Statins versus Other Lipid Therapies (COMPELL) study of 292 patients at high risk of MI and with mixed dyslipidemia (mean baseline LDL-C, 197 mg/dL [5.10 mmol/L]; HDL-C, 49 mg/dL [1.27 mmol/L]; and triglycerides, 168 mg/dL [4.35 mmol/L]) support this combination.<sup>67</sup> In this study, patients were randomized to treatment with either ER niacin (1 to 2 g daily) plus moderate doses of a statin (rosuvastatin, 10 to 20 mg daily, or atorvastatin, 20 to 40 mg daily), high-dose statin therapy (rosuvastatin, 20 to 40 mg daily), or combination therapy with simvastatin and ezetimibe (20/10 mg increasing to 40/10 mg daily). Although all treatments lowered LDL-C and non-HDL-C levels by about 50% or more, the combination of niacin plus statins resulted in substantially greater decreases in triglyceride levels and up to 3.5-fold greater increases in HDL-C levels than with the other regimens. Despite demonstrable improvements in the lipid profile, the role of niacin in lipid management has been questioned. Several large trials failed to show significant improvement.<sup>68</sup>

## Fibrate

The fibrates, gemfibrozil and fenofibrate, are peroxisome proliferator receptor- $\alpha$  agonists used for treating hypertriglyceridemia and to increase HDL-C.<sup>69</sup> The therapeutic effect of these drugs is a 25% to 50% decrease in triglyceride levels and a 5% to 15% increase in HDL-C. In addition, fenofibrate may also decrease LDL-C by 10% to 20%, whereas an increase in LDL-C is often seen when gemfibrozil is used to treat very high levels of triglycerides. Gemfibrozil is taken 30 minutes before morning and evening meals as a 600-mg tablet. Fenofibrate is started

at 54 mg by mouth with food once daily, and the dosage can be increased to 160 mg daily. Several trials demonstrated reduction in the progression of atherosclerosis but had no impact on decreasing mortality.<sup>70,71</sup>

## Bile Acid Sequestrants

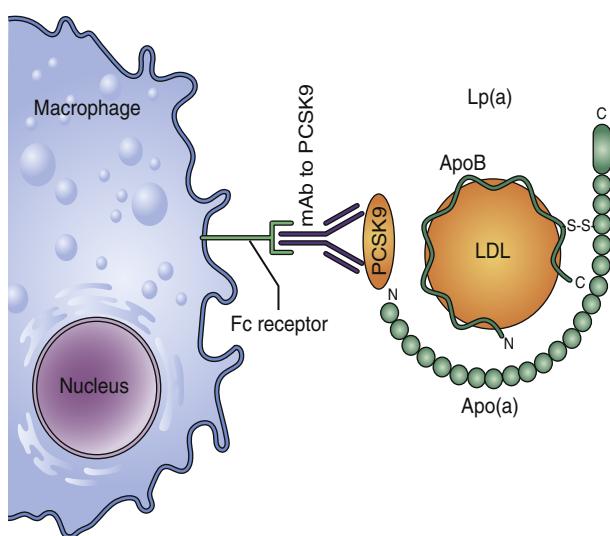
Bile acid sequestrants include colestipol, cholestyramine, and a more recently developed form, colesevelam. Historically, cholestyramine and colestipol were among the first drugs available to treat high TC and LDL-C. These drugs may be used as monotherapy in concert with dietary modification to achieve enhanced LDL-C lowering, but are more often used in combination with statin therapy. As noted earlier, doubling the dose of a statin may achieve only a 6% further reduction in LDL-C, but adding a sequestrant to a statin can further lower LDL-C by 12% to 16%.<sup>72</sup> Sequestrants have extremely low rates of systemic toxicity. Dyspepsia and constipation are known side effects. Colesevelam (WelChol, Daiichi-Sankyo, Inc., Basking Ridge, NJ) has significantly reduced these side effects and increased the compliance in the use of these drugs. It also has the advantage of being formulated as a tablet. Colesevelam comes in 625-mg tablets and should be started at three tablets twice daily with meals followed by liquid. In addition to the previously listed GI side effects, bile acid sequestrants may significantly increase triglycerides and are known to bind certain other drugs in the GI tract.

## Ezetimibe

Ezetimibe is the first in a new class of pharmacologic agents for reducing TC and LDL-C. It specifically interferes with the absorption of cholesterol from the GI tract and results in a 15% to 20% reduction in LDL-C as monotherapy.<sup>73</sup> Ezetimibe is often used with a statin to achieve a further reduction in LDL-C of 20% to 25%, with added beneficial effects on triglycerides and HDL-C. The efficacy of ezetimibe in reducing atherosclerosis has been questioned, but the National Lipid Association endorsed its use because of its proven efficacy.<sup>74</sup>

## Omega-3 Fatty Acids

Polyunsaturated fatty acids of the omega-3 type are found in fish and other marine animals, as well as in soybeans and other vegetables. Varying strength of evidence exists to support consumption of omega-3 fatty acid. ATP III supports the AHA's recommendation that fish, particularly fish high in omega-3 fatty acids, be included as part of a CHD risk reduction diet.<sup>75</sup> Fish is also low in saturated fat and may be cardioprotective. A number of observational studies have suggested that regular consumption of fish reduces the risk for CHD.<sup>76,77</sup> An Italian trial showed that the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) at a dose of 1 g daily reduced the risk of sudden death.<sup>78</sup> Other trials showed mixed results.<sup>79-81</sup> It is important to note that higher doses of EPA and DHA, 3 g or more daily, have a significant



**Figure 13.7** Mechanism of action of proprotein convertase subtilisin/kexin type-9 (PCSK9) to decrease low-density lipoprotein (LDL). *Apo(a)*, Apolipoproteins (a); *Lp(a)*, lipoprotein (a). (From Shapiro MD, Fazio S. From lipids to inflammation: new approaches to reducing atherosclerotic risk. *Circ Res*. 2016;118(4):732–749.)

hypotriglyceridemic effect without significant adverse events. However, more definitive trials are necessary before strongly recommending high doses of omega-3 fatty acids.

### Cholesterol Ester Transfer Protein Inhibitors

In addition to lowering LDL-C, the ability to raise HDL-C is a tangible therapeutic target. Endogenously, the transfer of cholesterol ester from HDL-C to apo B-containing lipoproteins, VLDL, and LDL, in exchange for triglycerides is mediated by CETP. This is deemed a heterotypic transfer. Homotypic transfer or the transfer of cholesteryl ester between HDL subtypes is also mediated by CETP. Of the developed CETP inhibitors, torcetrapib and anacetrapib inhibit both homotypic and heterotypic transfer, whereas dalcetrapib inhibits only heterotypic transfer.<sup>82</sup>

### PCSK9 Inhibitors

Protein convertase subtilisin/kexin type-9 (PCSK9) increases LDL by interfering with hepatic LDL receptor recycling (Fig. 13.7). Monoclonal antibodies directed against PCSK9 inhibitors, have been effective in lowering LDL by 60% in patients.<sup>83</sup> Large multicenter trials (FOURIER, ODYSSEY OUTCOMES) have shown that LDL-C can be significantly decreased by these agents to 25–50 mg/dL. The former trials also confirmed the relative risk reduction of myocardial infarction, stroke and death from cardiovascular causes.<sup>84</sup> PCSK9 inhibitors are recommended for patients who have severe adverse

reactions to statins or in patients with insufficient lowering of LDL-C when on a maximum dose of statin plus ezetimibe. The FDA has approved alirocumab and evolocumab in patients with clinical ASCVD or heterozygous familial hypercholesterolemia.

### Novel Therapeutic Agents

Inclisiran is an interfering RNA targeting PCSK9 messenger RNA leading to the inhibition of PCSK9 synthesis. The benefit of such an agent is a lower dose frequency than what is needed with monoclonal antibodies. Several trials are currently in phase 2 or 3 to see if inclisiran can reduce major CV events in patients with ASCVD.

Bempedoic acid inhibits ATP citrate lyase which up-regulates LDL receptors by reduction in cholesterol synthesis. The enzyme required with the active metabolite is not present in myocytes, so that a potential benefit of this drug is the lack of muscular pain associated with statins. This agent is also in early clinical trials to assess its safety and efficacy.

AKCEA-APO(a)-L<sub>Rx</sub> is an antisense oligonucleotide targeting lipoprotein(a). It can lead to significant reduction in lipoprotein(a), up to 90%, and was safe to administer in early trials. Monoclonal antibodies or antisense oligonucleotides targeting angiopoietin-like 3 are also being investigated.<sup>84</sup>

### Combination Drug Therapy

Combination therapy has been shown to be effective in obtaining LDL, HDL, and triglyceride targets in patients with dyslipidemia. A combination of a statin plus an agent that blocks the intestinal absorption of cholesterol is particularly effective in decreasing LDL-C levels. Both ezetimibe and the bile acid sequestrants can be safely added to the maximal dose of a statin or can be used with lower doses to reach LDL-C therapeutic goals. Some patients will not tolerate the maximal dose of any statin, and one or both of these intestinally acting agents will allow the attainment of LDL-C goals when added to a submaximal dose of a statin. In addition, ER niacin can be combined with a statin or one of the intestinally acting drugs, or can be used in combination with both classes of drugs to reach LDL-C targets in patients with very high LDL-C levels, such as those with heterozygous familial hypercholesterolemia. Statin therapy may also be combined with fenofibrate, niacin, or omega-3 fatty acids to achieve control in patients with combined hyperlipidemia; the combination yields superior results over monotherapy. In general, gemfibrozil should not be used with a statin because of its inhibition of statin metabolism, which increases the potential toxicity of all statins.<sup>85</sup> Fenofibrate is a better choice when statin and fibrate combination therapy is required.<sup>86</sup> The SANDS (Stop Atherosclerosis in Native Diabetics) trial used the endpoint of change in CIMT as a surrogate for the control of atherosclerosis. In the most aggressive group with lipid goals of less than 70 mg/dL (1.81 mmol/L) for LDL-C and less than 100 mg/dL (2.59 mmol/L) for non-HDL-C, CIMT regression was achieved. However,

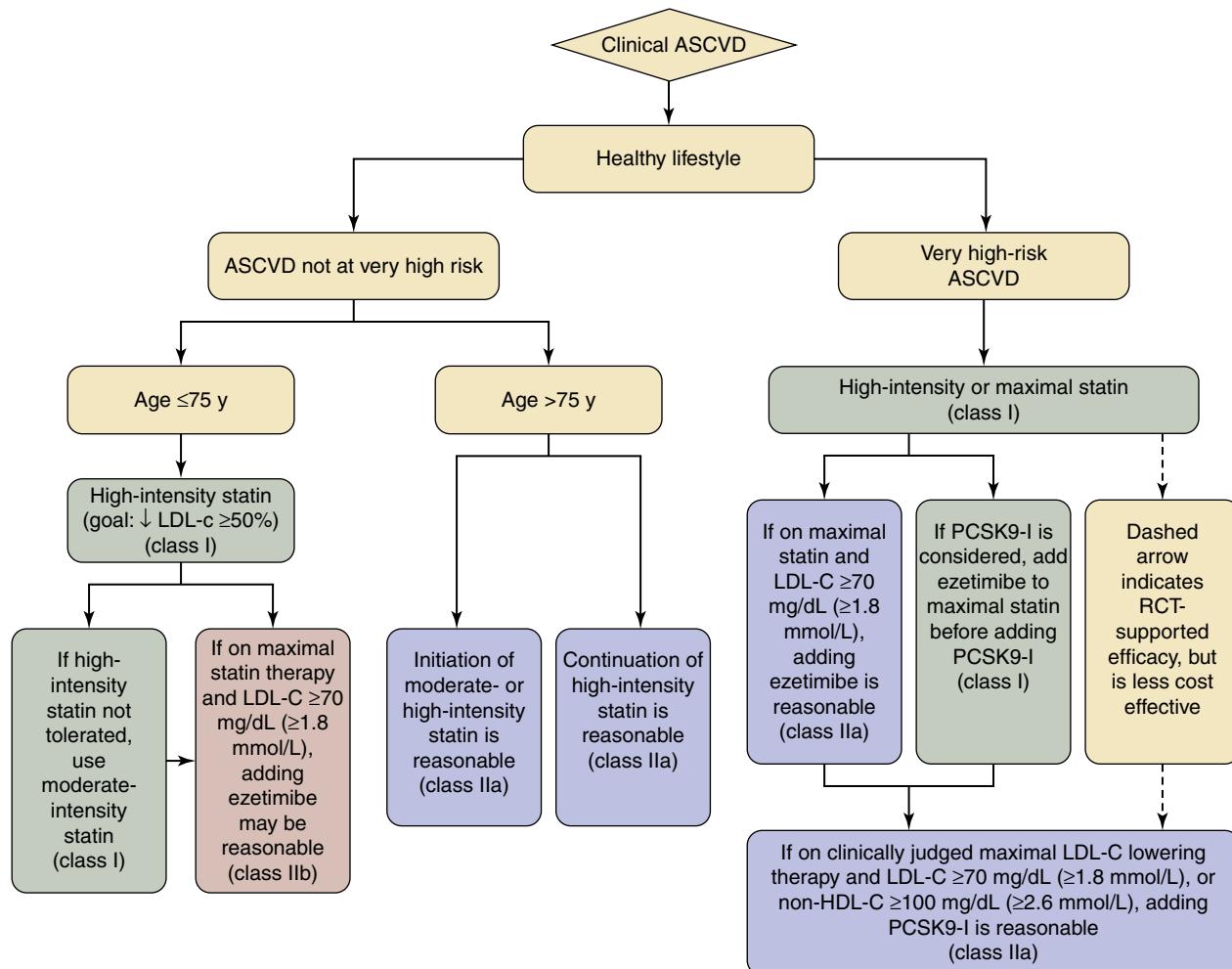
larger prospective studies with clinical endpoints that include cardiovascular morbidity and mortality and PAD-related outcomes are still needed to evaluate the outcome benefits of combination therapy.

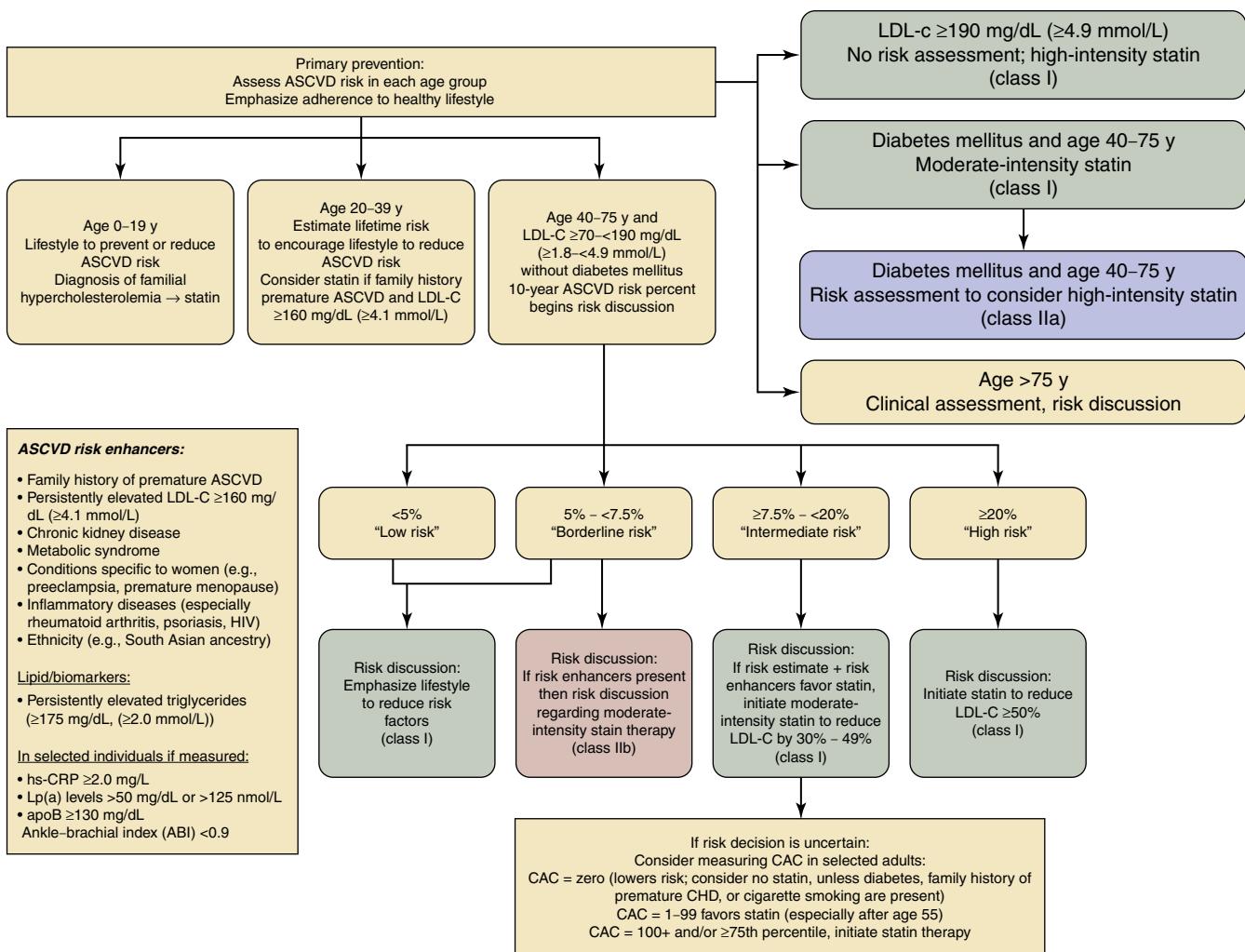
### Homozygous Familial Hypercholesterolemia

In 1972, Goldstein and Brown treated two young siblings, aged 6 and 8, who were hospitalized at the NIH for acute coronary syndromes due to LDL levels eightfold above normal. They were diagnosed with homozygous familial hypercholesterolemia (HFH) and became the impetus for scientists to

elucidate the LDL receptor mechanism.<sup>2</sup> Even with combination therapy, patients with HFH have a difficult time reducing LDL. LDL apheresis is available in some clinical centers and may be used when high-risk patients fail to meet target goals, despite dietary management and maximum tolerated lipid-lowering regimens. In addition, lomitapide, a microsomal triglyceride transfer protein inhibitor, and mipomersen, an antisense oligonucleotide inhibitor of apo B-100 synthesis, have been approved, but are presently available only through Risk Evaluation and Mitigation Strategy (REMS). Now PCSK9 inhibitors have been shown to effectively reduce LDL levels in HFH patients.<sup>83</sup>

## CHAPTER ALGORITHMS





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Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus, Vascular Disease Foundation, et al. ACC/AHA 2005 Practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association of Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology and the ACC/AHA Task Force on Practice Guidelines (writing committee to develop guidelines for the management of patients with peripheral arterial disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation.* 2006;113:e463–e654.

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A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com).

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# Hypertension

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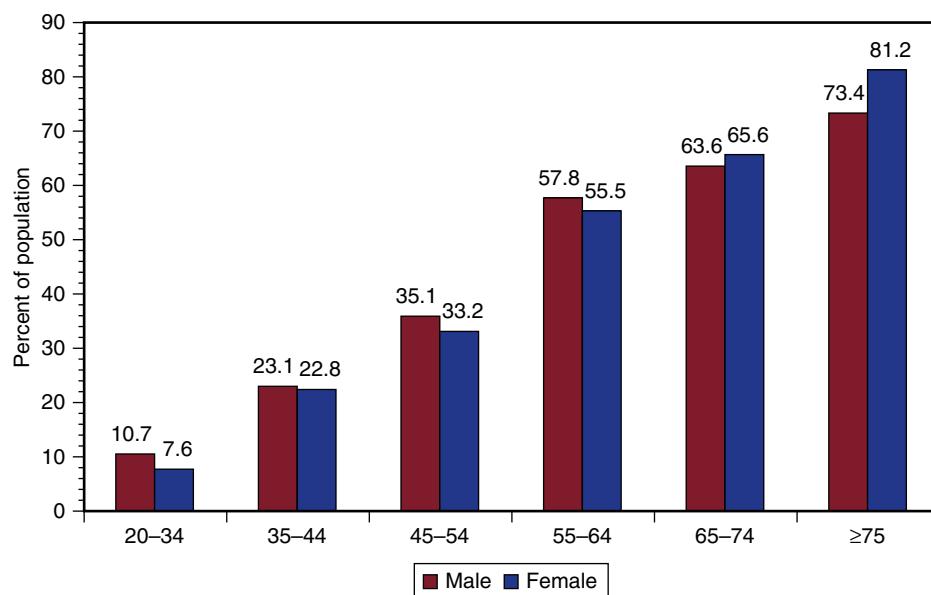
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Hypertension is a key risk factor in the pathophysiology of atherosclerosis and the development of cardiovascular diseases (CVD) including peripheral artery disease (PAD). Available evidence related to PAD and hypertension is largely extrapolated from subgroup analyses of larger trials of patients with atherosclerotic vascular disease and cardiovascular risk factors. Consequently, there are no current concrete within-class comparison studies of the effects of the treatment of hypertension on PAD-related disease outcomes. Despite the lack of prospective, randomized clinical trial data showing that antihypertensive pharmacotherapy alters the course of PAD, blood pressure control is recommended to minimize the risk of CVD and cerebrovascular disease.

## EPIDEMIOLOGY

### Scope of the Problem

The 2017 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines indicated that nearly half of all adults in the US have hypertension.<sup>1</sup> Hypertension, a modifiable risk factor, is the leading cause of CVD deaths and is second only to cigarette smoking as a preventable cause of mortality overall.<sup>2,3</sup> The prevalence of hypertension increases with age and affects Black Americans more than White (Fig. 14.1). The risk of hypertension-related CVD events, including ischemic heart disease, heart failure, and cerebrovascular



**Figure 14.1** Prevalence of high blood pressure in adults  $\geq 20$  years of age by sex and age (NHANES 2011–2014). (Reprinted with permission. *Circulation*. 2018;137:e67–e492. ©2018 American Heart Association, Inc.)

disease, increase with age. Further, HTN-related CVD events are over 10% greater in women than men, and are 15% greater among Black than White Americans.<sup>3,4</sup>

The CArdiovascular research using LInked Bespoke studies and Electronic health Records (CALIBER) study investigated the association between systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements and 12 cardiovascular disorders in 1.25 million adults.<sup>5</sup> Elevated DBP had a greater effect on abdominal aortic aneurysms (AAA), whereas increased SBP was the strongest predictor for intracerebral and subarachnoid hemorrhage, myocardial infarction, angina, and PAD. A 2019 meta-analysis determined that hypertension increases the relative risk of developing an AAA by 66%, raising the risk by 14% and 28% for every 20 mm Hg and 10 mm Hg increase in SBP and DBP.<sup>6</sup> Quantifying the risk of PAD among patients with elevated BP depends, in part, upon the definition of PAD. For example, data from the Framingham Heart Study, which defined PAD by intermittent claudication, showed that the risk of developing PAD increases with increasing SBP and DBP in both men and women.<sup>7</sup> Other studies, using ankle–brachial index (ABI) to define PAD, demonstrated slightly different associations, implicating elevations in SBP more than elevations in DBP in risk of declining ABIs.<sup>8,9</sup> Long-term 38-year follow-up data from the original Framingham Heart Study cohort and National Health and Nutrition Examination Survey (NHANES) study demonstrated that untreated and uncontrolled hypertension were associated with a twofold increase in the risk of PAD development, defined by either claudication or ABI.<sup>10–13</sup> Overall, elevated hypertension contributed to the risk of PAD; however, the association between CVD, which includes PAD, and SBP appears to be the strongest.

Over the past decade, the mounting evidence from these and other studies provided the impetus for the ACC/AHA to reframe the definition of hypertension from the previously accepted Joint National Committee (JNC) guidelines. The prior JNC 7 guidelines defined four BP categories: (1) normal; (2) prehypertension; (3) stage 1 hypertension; and (4) stage 2

hypertension (Table 14.1).<sup>14</sup> The CVD risk in the setting of severe hypertension (i.e., SBP > 160 mm Hg) is very well established. Over the last 50 years, the awareness, treatment, and control of hypertension have steadily improved. As a result, the prevalence of severe hypertension and the associated CVD events were declining.<sup>1,15,16</sup> However, since the early 2000s, the NHANES estimates that improvements in hypertension-associated morbidity and mortality have stabilized.<sup>17</sup> This dichotomy may be explained by multiple recent studies focused on the risks associated with mild to moderate BP elevations that were not defined as hypertension in JNC 7. The Systolic Blood Pressure Intervention Trial (SPRINT) included 9361 patients with hypertension and elevated CVD risk but without diabetes. Patients were assigned to a SBP target of <120 mm Hg or a target of <140 mm Hg. The primary outcome was a composite of myocardial infarction, acute coronary syndrome, heart failure, or death from cardiovascular causes. The trial was notably stopped early due to significantly lower rates of fatal and nonfatal major CVD events as well as death from any cause in the SBP <120 mm Hg target group.<sup>18</sup> In the UKPDS trial, which examined tight BP control in patients with hypertension and diabetes, tight BP control was associated with reduced risk of death related to diabetes and the onset of diabetes-related complications, diabetic retinopathy and deterioration in visual acuity.<sup>19</sup> The Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD) trial evaluated 4733 diabetic patients with or without intensive blood glucose control and found no reduction in the composite of nonfatal myocardial infarction, stroke, or death from CVD when targeting a SBP <120 mm Hg as compared to <140 mm Hg overall.<sup>20</sup> However, ACCORD did establish that SBP <120 mm Hg reduced the composite primary outcome for the subgroup without intensive blood glucose and stroke overall, comparable to SPRINT.<sup>21</sup> Further, data from these trials and others were synchronized within multiple meta-analysis, indicating that even a SBP/DBP of 120–129/80–84 mm Hg, when compared to <120/80 mm Hg, increased the relative risk of CVD events by

**TABLE 14.1** Diagnosis of Hypertension

Blood Pressure Category	JNC 7 2003			ACC/AHA 2017							
	SBP, mm Hg		DBP, mm Hg	Management	Initial Drug Therapy		SBP, mm Hg	DBP, mm Hg	Management	Lifestyle Modification	Initial Drug Therapy
	Lifestyle Modification <sup>c</sup>	Without Compelling Indication	With Compelling Indication <sup>a</sup>						10-year CVD risk <10% <sup>d</sup>	10-year CVD risk ≥10% <sup>d</sup>	
<b>Normal</b>	<120	and	<80	Encouraged			<120	and	<80	Encouraged	Reassess in 1 year
<b>Elevated<sup>b</sup></b>	130–139	or	80–89	Yes	None	1-Drug	120–129	and	<80	Yes	Reassess in 3–6 months
<b>Hypertension</b>											
<b>Stage 1</b>	140–159	or	90–99	Yes	1-Drug	Alternative or additions as indicated	130–139	or	80–89	Yes	Reassess in 3–6 months 1-Drug
<b>Stage 2</b>	≥160	or	≥100	Yes	2-Drug combination		≥140	or	≥90	Yes	1- or 2-Drug combination

<sup>a</sup>Chronic kidney disease and/or diabetes mellitus<sup>b</sup>Category defined as prehypertension in JNC 7<sup>d</sup>Atherosclerotic cardiovascular disease (ASCVD) risk calculator available online: <http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/><sup>c</sup>Lifestyle modifications, prescribed as nonpharmacologic therapy, are described in Table 14.6

ACC, American College of Cardiology; AHA, American Heart Association; CVD, cardiovascular disease; DBP, diastolic blood pressure; JNC, Joint National Committee; SBP, systolic blood pressure.

nearly 50%.<sup>22–26</sup> Therefore, the stagnation in CVD reduction over time, in the face of improved awareness and treatment, suggests potential mis-identification and treatment of patients with mild to moderately elevated BP. These findings fueled the recent re-categorization of hypertension by the ACC/AHA.

The 2017 ACC/AHA guidelines lowered the BP threshold required for a diagnosis of hypertension in an attempt to further improve outcomes across the four categories. The updated definition of stage 1 hypertension includes those previously diagnosed with pre-hypertension (JNC 7), while stage 2 hypertension encompasses both previous categories of hypertension (Table 14.1). The new categorization increased the prevalence of hypertension in the US by 13.7%, but this only increased the recommendation for pharmacologic therapy by 1.9%. However, among patients with SBP of 130–139 and DBP of 80–89, nearly one third were newly recommended for antihypertensive pharmacotherapy.

In summary, hypertension is prevalent in the adult US population and is a major risk factor for atherosclerotic diseases, specifically PAD. Hypertension and PAD both independently and synergistically confer an increased risk of CVD morbidity and mortality. Evidence-based societal guidelines have been recently updated to alter both the diagnosis and management of hypertension to continue to improve associated morbidity and mortality and constitute an important target for patients with PAD.<sup>1,8</sup>

## DIAGNOSIS

### Definition of Hypertension

Previous epidemiologic studies and therapeutic trials have used different criteria to define hypertension in populations. As discussed above, the definition of hypertension was significantly modified as the expert guidelines transitioned from the JNC 7 to the new ACC/AHA guidelines (Table 14.1). These new guidelines differ from the current European Society of Cardiology and European Society of Hypertension (ESC/ESH) and National Institute for Health and Care Excellence (NICE) guidelines, which define hypertension with in-office BP measures of SBP 140 mm Hg or DBP 90 mm Hg.<sup>27</sup> The ACC/AHA currently recommends diagnostic BP measurements be based on the average of two to three properly measured, seated readings on each of two to three separate occasions.<sup>1</sup> In a systematic review completed by the US Preventative Services Task Force in 2015, ambulatory BP monitoring better predicted CVD events than in-office BP measurements.<sup>28</sup> Therefore, out-of-office BP measurements are recommended to both confirm the in-office diagnosis of sustained hypertension as well as to monitor the response to treatment.

Ambulatory BP monitoring allows for accurate differentiation between sustained, masked, and white coat hypertension. As the name implies, sustained hypertension is diagnosed when BP measurements are consistently elevated independent of the testing environment. Masked hypertension is defined by normal in-office and elevated out-of-office BP measurements. Although more difficult to detect, masked hypertension is

associated with an increased risk of CVD equal to or even greater than those with sustained hypertension. Therefore, masked hypertension is treated in the same manner as for sustained. In contrast, approximately 25% of Americans have elevated in-office BP measurements with corresponding normal out-of-office BPs. This represents white coat hypertension which confers CVD risk equal to that of controlled hypertension. White coat hypertension may be treated with lifestyle modifications and careful monitoring for evolution to sustained hypertension.<sup>1,29</sup>

### Blood Pressure Measurement Technique

Accurately monitoring and measuring BP is essential for the correct classification of the severity of hypertension to both quantify the potential CVD risk and guide evidence-based therapies to minimize those risks. All adults should be screened for hypertension with routine BP measurements following a simple set of six steps to ensure proper technique (Table 14.2). In patients with PAD, BP should be assessed in both arms to identify subclavian or innominate arterial stenoses that may contribute to erroneous low BP measurements.<sup>30</sup>

Out-of-office BP monitoring can be completed accurately with one of two techniques. Ambulatory BP monitoring is automated and programmed to occur at 15- to 30-minute intervals over a 24-hour period. Home BP monitoring, although less rigorous, is more practical. Recommended home BP monitoring procedures include two readings, more than one minute apart, taken before breakfast and before supper, all recorded by an automated BP monitor storing the readings.<sup>1</sup> The 2017 ACC/AHA guidelines quantify the definition of hypertension with ambulatory monitoring with one of three SBP/DBP criteria: (1) 24-hour mean 125/75 mm Hg; (2) awake mean 130/80 mm Hg; or (3) sleep mean 110/65 mm Hg.<sup>1</sup>

### Primary Causes

Arterial BP represents both cardiac output and systemic vascular resistance, responding to moment to moment and cumulative environmental exposures within the context of genetic influences. The pathogenesis of primary hypertension, formally essential hypertension, is poorly understood but has a number of known risk factors. Specifically, advancing age, obesity, family history, black race, Hispanic ethnicity, a high sodium and/or low potassium diet, physical inactivity, and excessive alcohol intake are all strongly and independently associated with the gradual and progressive rise in BP resulting in primary hypertension.<sup>4,16,31</sup>

### Secondary Causes

A distinct remediable cause of hypertension can be identified in approximately 10% of patients.<sup>32</sup> Upon identification, effective treatment of the underlying cause can markedly reduce BP and the associated risk of CVD. Therefore, all patients should undergo a thorough history and physical exam to differentiate primary from secondary hypertension.

**TABLE 14.2** Accurate Measures of Blood Pressure

Key Steps for Proper Blood Pressure Measurements	Specific Instructions
<b>Step 1: Properly prepare the patient</b>	<ol style="list-style-type: none"> <li>1. Have the patient relax, sitting in a chair (feet on floor, back supported) for &gt;5 minutes.</li> <li>2. The patient should avoid caffeine, exercise, and smoking for at least 30 minutes before measurement.</li> <li>3. Ensure patient has emptied his/her bladder.</li> <li>4. Neither the patient nor the observer should talk during the rest period or during the measurement.</li> <li>5. Remove all clothing covering the location of cuff placement.</li> <li>6. Measurements made while the patient is sitting or lying on an examining table do not fulfill these criteria.</li> </ol>
<b>Step 2: Use proper technique for blood pressure measurements</b>	<ol style="list-style-type: none"> <li>1. Use a blood pressure measurement device that has been validated, and ensure that the device is calibrated periodically.</li> <li>2. Support the patient's arm (e.g., resting on a desk).</li> <li>3. Position the middle of the cuff on the patient's upper arm at the level of the right atrium (the midpoint of the sternum).</li> <li>4. Use the correct cuff size, such that the bladder encircles 80% of the arm, and note if a larger- or smaller-than-normal cuff size is used.</li> <li>5. Either the stethoscope diaphragm or bell may be used for auscultatory readings.</li> </ol>
<b>Step 3: Take the proper measurements needed for diagnosis and treatment of elevated blood pressure/hypertension</b>	<ol style="list-style-type: none"> <li>1. At the first visit, record blood pressure in both arms. Use the arm that gives the higher reading for subsequent readings.</li> <li>2. Separate repeated measurements by 1–2 minutes.</li> <li>3. For auscultatory determinations, use a palpated estimate of radial pulse obliteration pressure to estimate SBP. Inflate the cuff 20–30 mm Hg above this level for an auscultatory determination of the blood pressure level.</li> <li>4. For auscultatory readings, deflate the cuff pressure 2 mm Hg per second, and listen for Korotkoff sounds.</li> </ol>
<b>Step 4: Properly document accurate blood pressure readings</b>	<ol style="list-style-type: none"> <li>1. Record SBP and DBP. If using the auscultatory technique, record SBP and DBP at onset of the first Korotkoff sound and disappearance of all Korotkoff sounds, respectively, using the nearest even number.</li> <li>2. Note the time of most recent blood pressure medication taken before measurements.</li> </ol>
<b>Step 5: Average the readings</b>	Use an average of ≥2 readings obtained on ≥2 occasions to estimate the individual's level of blood pressure.
<b>Step 6: Provide blood pressure readings to patient</b>	Provide patients with the SBP/DBP readings both verbally and in writing.

DBP, diastolic blood pressure; SBP, systolic blood pressure.

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In conjunction with a full medical, social, and family history, a complete review of over-the-counter and prescribed substances or medications is required (Table 14.3). The physical examination of patients with suspected secondary hypertension should include auscultation for abdominal bruits, palpation of the thyroid gland, and assessment of pulses in the upper and lower extremities. Patients with new onset hypertension should undergo basic laboratory testing for risk factor stratification, potential causes, and end organ damage. Routine testing should include a lipid panel, fasting glucose, complete blood count, thyroid-stimulating hormone, electrolytes (i.e., sodium, potassium, and calcium), serum creatinine with estimated glomerular filtration rate, urinalysis, and electrocardiogram. The results of these examinations determine if further evaluation for causes of secondary hypertension (Table 14.4) require investigation. Plasma renin and aldosterone, cortisol and metanephrine levels, uric acid levels, and echocardiogram or visceral arterial duplex are not universally recommended but may be useful in identification of secondary causes.

Following initial diagnosis and treatment of presumed primary hypertension, patients with resistant hypertension should be reevaluated for causes of secondary hypertension. In 2018, the AHA modified the criteria for resistant hypertension (Table 14.5) to help identify and recommend treatment for this subset of patients who possess a twofold higher risk of CVD than those with controlled hypertension.<sup>32</sup>

## HYPERTENSION AND ATHEROSCLEROSIS

The association of hypertension with the development of atherosclerosis has long been known, but the molecular and mechanical mechanisms involved are not completely understood. This is likely due to the complex pathogenesis of atherosclerosis. Many factors contribute to the development of atherosclerosis, including genetics, behavioral tendencies (e.g., smoking), environmental factors, and comorbid conditions (e.g., diabetes mellitus and hyperlipidemia).

**TABLE 14.3** Medications Which May Increase Blood Pressure

Agent	Possible Management Strategy
Alcohol <sup>a</sup>	Limit daily intake to ≤1 for women and ≤2 for men
Amphetamines (e.g., amphetamine, methylphenidate, dexamphetamine, dextroamphetamine)	Discontinue use or decrease dose
Antidepressant (e.g., MOI, SNRI, TCA)	Discontinue use or decrease dose Consider transition to SSRI Avoid tyramine-containing foods with MAOIs
Atypical antipsychotics (e.g., clozapine, olanzapine)	Discontinue use or decrease dose Consider transition to alternatives with less risk of weight gain Consider lifestyle modifications to minimize weight gain
Caffeine	Discontinue use or decrease dose to <300 mg/day
Decongestants (e.g., phenylephrine, pseudoephedrine)	Discontinue use, minimize duration of exposure, or decrease dose
Herbal supplements (e.g., Ma Huang, St. John's wort)	Discontinue and avoid use
Immunosuppressants (e.g., cyclosporine, tacrolimus)	Consider transition to alternative medications Treatment with calcium channel blockers
Oral contraceptives and hormone replacement	Use low-dose (<30 µg ethinyl estradiol) or progestin-only forms of contraception Consider alternative forms of birth control
Nonsteroidal anti-inflammatory agents	Discontinue and avoid use
Recreational drugs (e.g., cocaine, methamphetamines, etc.)	Discontinue and avoid use
Systemic corticosteroids	Avoid or limit use Consider inhaled and/or topical administration routes
Angiogenesis inhibitors (e.g., bevacizumab) and tyrosine kinase inhibitors (e.g., sunitinib, sorafenib)	Initiate or intensify anti-hypertensive therapies

<sup>a</sup>One drink contains approximately 14 g of pure alcohol and represents 12 oz of regular beer (5% alcohol), 5 oz of wine (12% alcohol), and 1.5 oz of spirits (40% alcohol). Table data content recapitulated and adapted from the Table 14.16 of the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines<sup>1</sup> in combination with Resistant Hypertension: Detection, Evaluation, and Management: A Scientific Statement From the American Heart Association.<sup>32</sup>

**TABLE 14.4** Causes of Secondary Hypertension

Cause	Signs and Symptoms
Aortic coarctation	Young patients with hypertension (<30 years of age), disparate blood pressures in upper and lower extremities, absent femoral pulses, continuous murmur over back or chest, abdominal bruit
Obstructive sleep apnea	Resistant hypertension with loss of normal nocturnal blood pressure fall, obesity, snoring, hypersomnolence
Renal artery stenosis (atherosclerotic or fibromuscular dysplasia)	Abrupt onset and difficult to control hypertension, fibromuscular dysplasia (women), flash pulmonary edema, abdominal or other vascular bruits
Renal parenchymal disease	Fatigue, edema, urinary tract infections, falling estimated glomerular filtration rate, proteinuria
Prostatism (post-renal urinary tract obstruction)	Urinary frequency and nocturia, declining estimated glomerular filtration rate
Hyperthyroidism	Warm and/or moist skin, heat intolerance, nervousness, tremulousness, insomnia, weight loss, fatigue, proximal muscle wasting
Hypothyroidism	Dry skin, cold intolerance, constipation, hoarseness, weight gain
Primary aldosteronism	Resistant hypertension, muscle cramps, weakness, hypokalemia, advanced cardiac (especially atrial fibrillation), renal disease, incidentally discovered adrenal mass
Cushing syndrome	Rapid weight gain, depression, central obesity, facial rounding (moon faces), supraclavicular fat pads, easy bruising, wide (1-cm) striae
Pheochromocytoma/paraganglioma	Labile blood pressure, headaches, and episodic tachycardia, sweating, pallor, dizziness, incidentally discovered adrenal mass, stigmata of neurofibromatosis (i.e., café-au-lait spots)
Medications	See Table 14.3
Others:	Primary hyperparathyroidism, congenital adrenal hyperplasia, mineralocorticoid excess syndromes, acromegaly.

Table data content recapitulated and adapted from the Table 14.13 of the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines<sup>1</sup> in combination with Resistant Hypertension: Detection, Evaluation, and Management: A Scientific Statement From the American Heart Association.<sup>32</sup>

**TABLE 14.5****Four Required Criteria for Diagnosis of Resistant Hypertension**

Resistant Hypertension Diagnosis <sup>32</sup>	
<b>1</b>	Blood pressure measure, diagnostic categories, and treatment goals are in accordance with current guidelines ( <a href="#">Table 14.1</a> )
<b>2</b>	Blood pressure elevations despite 3 antihypertensive agents including a long-acting calcium channel blocker, blocker of the renin–angiotensin system (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers), and diuretic all at maximum or maximally tolerated doses
<b>3</b>	Blood pressure elevations are sustained and not representative of white coat hypertension
<b>4</b>	Blood pressure elevations are not secondary to medication nonadherence

Renal artery stenosis (RAS) is a cause of secondary hypertension and is commonly due to aortic and renal artery atherosclerosis, and should be included in the evaluation of patients with resistant hypertension. In a prospective cohort of 629 consecutive patients with PAD undergoing digital subtraction angiography, renal artery disease was found in 33%, with 9.6% having significant RAS (60%).<sup>33</sup> RAS reduces blood flow to the kidney and activates the renin–angiotensin–aldosterone system,<sup>34</sup> which is hypothesized to accelerate and promote further atherosclerosis in these patients, thus creating a vicious cycle. In addition, experimental models of RAS in pigs showed increased levels of oxidative stress which was a stimulus for atherosclerosis, independent of cholesterol levels.<sup>35</sup> Clinical evidence supports this hypothesis and may explain the high prevalence of RAS in patients with atherosclerosis in other arteries.

### Animal Models of Hypertension

Much insight into the interaction of hypertension and atherosclerosis has been gained from animal models. The models of hypertension include genetic (i.e., phenotype and genotype driven), surgical (i.e., renovascular or tissue injury), and environmental (i.e., endocrine, dietary, or vasoactive) models.<sup>36</sup> Previous research has demonstrated that hypertension can initiate inflammatory pathways that promote atheroma formation and increase atherosclerotic lesion size in mice.<sup>29</sup> Although not consistent throughout the literature, some mouse models further demonstrate that reducing BP was associated with reduced atherosclerosis.<sup>29</sup> These inconsistencies highlight the complex interplay between BP and development of atherosclerosis.

### Renin–Angiotensin System and Atherosclerosis

A theme that has consistently been observed in the literature is that manipulation of the renin–angiotensin system has a direct impact on atherosclerosis.<sup>37</sup> The renin–angiotensin system is responsible for control of arterial pressure, tissue perfusion, and extracellular volume. Renin is produced from the

juxtaglomerular cells in the nephron. Angiotensinogen, which is primarily synthesized in the liver, is converted to angiotensin I by renin. Angiotensin I is converted to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II is a potent vasoconstrictor, specifically on the efferent arteriole, and mediator of aldosterone secretion. Studies in mouse models have shown that chronic infusion of angiotensin II promoted while inhibition of the renin–angiotensin system decreased development of atherosclerosis independent of changes in arterial pressure.<sup>37,38</sup> Consequently, this axis is a prime target for pharmacotherapy directed at both hypertension and atherosclerosis.

A correlation between hypercholesterolemia and hypertension has been observed in humans. Vascular angiotensin II receptor type 1 (AT1) expression is upregulated in patients with hypercholesterolemia. Nickenig et al. administered angiotensin II to patients with hypercholesterolemia and those with normocholesterolemia and showed that the BP response was exaggerated in the hypercholesterolemia group.<sup>39</sup> Administration of statins mitigated this response.<sup>39</sup> Animal studies have shown that renin–angiotensin inhibition, in conjunction with statin therapy, reduced atherosclerosis and improved BP control as compared with renin–angiotensin inhibition alone.<sup>40,41</sup>

### Endothelial Dysfunction and Hypertension

Hypertension is associated with systemic endothelial dysfunction, which occurs early in the atherosclerotic process. Maintenance of normal endothelial function and appropriate physiologic vasodilation is important to both BP control as well as the development of atherosclerosis. Previous studies have shown that the presence of hypertension blunts the effects of an agonist-induced vasodilatory response.<sup>34</sup> Nitric oxide (NO) is a key endogenous vasodilator and is an essential product of normal endothelium that is critical to the vasodilator response. Reductions in endothelial-derived NO result in a reduced vasodilatory response, and may also contribute to the proinflammatory, prothrombotic, and procoagulant phenotype observed in atherogenesis. Vascular NO is synthesized by endothelial NO synthase (eNOS). The deletion of eNOS in mice significantly increased SBP and decreased heart rate as compared with wild-type controls,<sup>35</sup> supporting the importance of NO in BP regulation.

Although endothelial dysfunction is related to hypertension, the data regarding endothelial dysfunction as a precursor to hypertension is mixed. In one study, investigators evaluated forearm blood flow modifications by administering intrabrachial acetylcholine (endothelium-dependent vasodilator) and sodium nitroprusside (endothelium-independent vasodilator) to offspring of patients with primary hypertension.<sup>36</sup> The vasodilatory response to acetylcholine was blunted in the offspring from hypertensive parents, suggesting that an impairment in NO production may precede the onset of primary hypertension.<sup>36</sup> However, another study of young, Black adults with and without a family history of primary hypertension did not show a significant difference in brachial artery reactivity, and there was no evidence of early endothelial dysfunction among those with a family history of hypertension.<sup>37</sup> In this study,

women did exhibit more brachial artery vasodilation compared with men, irrespective of family history of hypertension. More research is needed to understand the role of endothelial dysfunction in the pathogenesis of hypertension.

## MANAGEMENT

### General Principles

The goal of treating hypertension is to lower BP with the associated reduction in atherosclerosis and CVD morbidity and mortality. Effective treatment of hypertension includes lifestyle modifications in conjunction with pharmacotherapy. For patients with stage 1 hypertension, the initiation of pharmacotherapy is guided by the 10-year atherosclerotic cardiovascular disease (ASCVD) risk calculator (<http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#/calculate/estimate/>).<sup>1</sup>

### Lifestyle Modifications

Lifestyle modifications, or nonpharmacologic therapies, are effective at lowering BP and reducing CVD risk.<sup>5,22</sup> The

relationship between weight loss and BP reduction appears to be linear. Every 1 kg of body weight reduction is associated with an approximate decrease in BP by 1 mm Hg.<sup>1</sup> Lifestyle modifications, including diet (e.g., the Dietary Approaches to Stop Hypertension (DASH) diet),<sup>42</sup> and exercise, improve overall health and reduce BP (Table 14.6).

### Antihypertensive Therapy

According to the NHANES, 82.7% of patients with hypertension were aware of their diagnosis and 75.6% were prescribed antihypertensives. However, only 51.8% of patients had their BP controlled.<sup>13</sup> Multiple randomized controlled trials demonstrated improving BP control reduces progression of lower extremity ischemia, improves endothelial cell function, and improves functional status in PAD patient subsets.<sup>43–45</sup> Yet optimal medical therapy, which includes BP control, is substantially worse among patients with PAD when compared to those without.<sup>4,46,47</sup>

Early data indicated calcium channel blockers (CCBs) or ACE inhibitors may reduce CVD events in those with PAD.<sup>43</sup> Yet, two large trials, Antihypertensive and Lipid-Lowering

**TABLE 14.6** Nonpharmacological Interventions

Nonpharmacological Intervention	Dose	Approximate Impact on Systolic Blood Pressure	
		Hypertension	Normotension
Weight loss	Weight/body fat	Best goal is ideal body weight, but aim for at least a 1-kg reduction in body weight for most adults who are overweight. Expect about 1 mm Hg for every 1-kg reduction in body weight.	-5 mm Hg -2/3 mm Hg
Healthy diet	DASH dietary pattern <sup>a</sup>	Consume a diet rich in fruits, vegetables, whole grains, and low-fat dairy products, with reduced content of saturated and total fat.	-11 mm Hg -3 mm Hg
Reduced intake of dietary sodium	Dietary sodium	Optimal goal is <1500 mg/day, but aim for at least a 1000 mg/day reduction in most adults.	-5 to 6 mm Hg -2 to 3 mm Hg
Enhanced intake of dietary potassium	Dietary potassium	Aim for 3500–5000 mg/day, preferably by consumption of a diet rich in potassium.	-4 to 5 mm Hg -2 mm Hg
Physical activity	Aerobic	90 to 150 minutes/week 65% to 75% heart rate reserve	-5 to 8 mm Hg -2 to 4 mm Hg
	Dynamic resistance	90 to 150 minutes/week 50% to 80%; 1 repetition maximum 6 exercises, 3 sets/exercise, 10 repetitions/set	-4 mm Hg -2 mm Hg
	Isometric resistance	3 sessions/week for 8 to 10 weeks 30% to 40% maximum voluntary contraction 4 × 2 minutes (hand grip), 1-minute rest between exercises	-5 mm Hg -4 mm Hg
Moderation of alcohol intake	Alcohol consumption <sup>b</sup>	In individuals who drink alcohol, reduce alcohol to: Men: ≤2 drinks/day Women: ≤1 drink/day	-4 mm Hg -3 mm Hg

<sup>a</sup>Dietary Approaches to Stop Hypertension (DASH) diet is low in fat and sodium and high in fruits and vegetables.<sup>42</sup>

<sup>b</sup>One drink contains approximately 14 g of pure alcohol and represents 12 oz of regular beer (5% alcohol), 5 oz of wine (12% alcohol), and 1.5 oz of spirits (40% alcohol).

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Treatment to Prevent Heart Attack Trial (ALLHAT) and International VErapamil-SR/Trandolapril (INVEST) studies, and associated meta-analyses demonstrated no significant differences by antihypertensive treatment classes in those with PAD.<sup>8,48,49</sup>

There has been a longstanding concern that antihypertensive pharmacotherapy may reduce limb perfusion in patients with PAD.<sup>50</sup> ALLHAT demonstrated hypertension was associated with a higher risk of PAD hospitalizations, procedures, and deaths.<sup>48</sup> INVEST reported a J-shaped curve where both lower and high SBP were associated with CVD events in those with PAD but not those without.<sup>49</sup> Therefore, especially given the 2017 ACC/AHA updated guidelines with lower BP goals (see Table 14.1), further investigation is required to refine the optimal BP target for patients with PAD.

## Pharmacotherapy

### General Considerations

All patients with elevated BP (>120/80) should be counseled regarding lifestyle modifications and nonpharmacologic therapies. This group has a high risk for progression to hypertension and increased risk of CVD morbidity and mortality. As first established in 1967 in a Veterans Administration Cooperative Study,<sup>51</sup> antihypertensive pharmacotherapies lowered BP and reduced the risk of CVD events, including cerebrovascular events, and all-cause mortality.<sup>52</sup> The ACC/AHA guidelines indicate pharmacotherapy should be initiated for either stage 1 hypertension and a 10-year ASCVD event risk >10% or stage 2 hypertension.<sup>1</sup> The overall recommended therapeutic BP goal is <130/80, but the ACC/AHA recognizes that additional reduction in CVD events may be achieved with a BP goal of <120/80.<sup>1</sup>

For initiation of antihypertensive pharmacotherapy, there are numerous medications available (Table 14.7). The specific class chosen for initiation should be tailored to each patient's age, comorbid conditions and concurrent medications, drug adherence, and out-of-pocket costs. First-line standard pharmacotherapy includes four medication classes: thiazide diuretics, CCBs, ACE inhibitors, and angiotensin II receptor blockers (ARBs).<sup>1</sup>

The ALLHAT trial randomized over 33,000 adults >55 years to first-line antihypertension pharmacotherapy including chlorthalidone (thiazide diuretic), amlodipine (CCB), lisinopril (ACE inhibitor), or doxazosin (alpha blocker). Chlorthalidone was overall superior to amlodipine for heart failure prevention. It was equivalent to amlodipine but superior to lisinopril for stroke prevention.<sup>53</sup> Doxazosin was inferior to all other medications and removed from randomization mid-trial. These patterns continue among black patients, in whom ACE inhibitors were found to be inferior to CCB in prevention of heart failure and stroke.<sup>54,55</sup> In summary, thiazide diuretics, CCB, ACE inhibitors, and ARBs all reduced the risk of CVD events. The largest clinical trial (ALLHAT) and some, but not all,<sup>52,56</sup> meta-analysis suggest long-acting thiazide diuretics (i.e., chlorthalidone) may be the optimal first-line antihypertensive pharmacotherapy.

For patients with stage 1 hypertension receiving pharmacotherapy, monotherapy in combination with lifestyle changes may be adequate. The overwhelming majority of patients are identified with stage 2 hypertension with an average BP more than 20/10 mm Hg above their goal. For these patients, pharmacotherapy initiation should include two first-line agents of different classes.<sup>14</sup> However, providers must consider the risk of and carefully monitor for hypotension and orthostatic hypotension, particularly among older adults. Drug combinations within the same (e.g., two CCBs) or similar (e.g., ACE inhibitor and ARBs) classes should be avoided. Some exceptions to this rule of thumb include concomitant use of both thiazide, potassium sparing, and loop diuretics as well as dihydropyridine and non-dihydropyridine CCBs.

For patients with other comorbid conditions, antihypertensive pharmacotherapy should be guided by the presence of stable and/or chronic ischemic heart disease, heart failure with or without a reduced ejection fraction, cerebrovascular disease, thoracic aortic disease, chronic kidney disease, and diabetes. Beta blockers effectively reduce angina pectoris, improve exercise times and ischemia, and prevent coronary events for patients with stable ischemic heart disease without heart failure.<sup>1,57</sup> Therefore, beta blockers, excluding atenolol, are recommended first-line pharmacotherapy in these patients with combination and escalation therapy. Among patients with heart failure, first-line and combination pharmacotherapy is driven by the associated ejection fraction. Patients diagnosed with stage 2 hypertension following an acute stroke, >72 hours from symptom onset and with stable neurologic status or transient ischemic attack, should follow standard antihypertensive pharmacotherapy initiation and combination. Hypertensive patients with chronic kidney disease and diabetes should receive standard antihypertensive pharmacotherapy unless albuminuria (300 mg/day or 300 mg/g of creatinine) is present. In the setting of albuminuria, ACE inhibitors should be considered as first-line pharmacotherapy and substituted for ARBs if not tolerated.<sup>58</sup> Although based largely on animal and observational studies, beta blockers were associated with improved survival and lower risk of operative repair for patients with thoracic aortic disease.<sup>59,60</sup> Finally, no specific antihypertensive medication class has shown superior benefit in patients with PAD.<sup>48,50</sup> Therefore, medications should be chosen based on other comorbidities.

### Thiazide Diuretics

Thiazide diuretics act in the distal convoluted tubule by blocking sodium and chloride transport. Thiazides tend to be more effective in patients with lower renin levels, which may be more common in Black patients and older hypertensive patients.<sup>61</sup> The beneficial effects of thiazides were established in the ALLHAT trial.<sup>53,55</sup> Given the low cost of thiazide diuretics, coupled with the prevention of both heart failure and stroke, the ALLHAT investigators and subsequent meta-analysis concluded that thiazide diuretics, especially long-acting chlorthalidone, should be considered the ideal first-line pharmacotherapy.<sup>53</sup> In addition, thiazide diuretics decrease calcium excretion and can prevent calcium-containing kidney stone formation and may

**TABLE 14.7** Antihypertensive Pharmacotherapy

Drug Class	Medications	Indications	Common Side Effects
<b>First-line standard pharmacotherapy</b>			
Thiazide diuretics	Chlorthalidone <sup>a</sup> Hydrochlorothiazide Indapamide Metolazone	Preferred first-line therapy due to superior CVD prevention. Use with caution in patients with a history of acute gout.	Hyponatremia, hypokalemia, hyperuricemia, hypercalcemia, insulin resistance, erectile dysfunction
Angiotensin-converting enzyme (ACE) inhibitors	Benazepril Captopril Enalapril Fosinopril Lisinopril Moexipril Perindopril Quinapril Ramipril Trandolapril	Preferred for chronic kidney disease and/or diabetes with evidence of proteinuria. Prevent recurrent atrial fibrillation. May cause acute kidney failure with severe bilateral renal artery stenosis. Do not use in combination with ARBs or in pregnancy.	Angioedema, cough, hyperkalemia (especially in patients with chronic kidney disease, on potassium supplements, or contaminate use of potassium-sparing medications)
Angiotensin II receptor blockers (ARBs)	Candesartan Eprosartan Irbesartan Olmesartan Losartan Telmisartan Valsartan	Preferred for chronic kidney disease and/or diabetes with evidence of proteinuria. May cause acute kidney failure with severe bilateral renal artery stenosis. Do not use in combination with ACE inhibitors or in pregnancy. Can be initiated >6 weeks after ACE inhibitor-associated angioedema.	Angioedema from ARB, hyperkalemia (especially with chronic kidney disease, potassium supplements, or contaminate use of potassium sparing medications)
Non-dihydropyridine calcium channel blockers (CCB)	Diltiazem Verapamil	May provide superior CVD prevention to ACE inhibitors and ARBs, particularly in Blacks. Avoid use with beta blockers due to increased risk of bradycardia and heart block. Do not use in heart failure with reduced ejection fraction.	Constipation, bradycardia, drug interactions (CYP3A4 inhibitor)
Dihydropyridine calcium channel blockers (CCB)	Amlodipine Clevidipine Felodipine Flunarizine Isradipine Levamldipine Nicardipine Nifedipine Nimodipine Nisoldipine	May provide superior CVD prevention to ACE inhibitors and ARBs, particularly in Blacks. Avoid in heart failure with reduced ejection fraction (use amlodipine or felodipine, if required).	Lower extremity edema (especially women), constipation, flushing
<b>Other Pharmacotherapy</b>			
Alpha blockers	Doxazosin <sup>b</sup> Prazosin <sup>b</sup> Terazosin <sup>b</sup> Phenoxybenzamine Phentolamine	Second-line agents with concomitant benign prostatic hypertrophy Management of pheochromocytoma	Orthostatic hypotension (especially elderly), tachycardia, dizziness, fatigue, sodium retention
Beta blockers	Acetbutolol Atenolol <sup>c</sup> Betaxolol <sup>c</sup> Bisoprolol <sup>c,d</sup> Carvediolol <sup>d</sup> Labetalol Metoprolol <sup>c,d</sup> Nadolol <sup>e</sup> Nebivolol Pindolol Propranolol <sup>e</sup> Sotalol	First-line therapy only with stable ischemic heart disease and heart failure. <sup>c</sup> Cardioselective <sup>b</sup> agents preferred and avoid noncardioselective <sup>d</sup> agents with reactive airway disease. Avoid abrupt cessation. Labetalol is recommended for treatment of hypertension in pregnancy.	Hyperlipidemia, bradycardia, insulin resistance

**TABLE 14.7** Antihypertensive Pharmacotherapy—cont'd

Drug Class	Medications	Indications	Common Side Effects
Central alpha agonists	Clonidine Methyldopa	Last-line therapy for resistant hypertension.	Rebound hypertension, central nervous system adverse effects, dry mouth, impotence
Loop diuretics	Bumetanide Ethacrynic acid Furosemide Torsemide	Preferred diuretics for symptomatic heart failure and advanced chronic kidney disease (eGFR <30 mL/min)	Hypokalemia, volume depletion
Potassium-sparing diuretics	Amiloride Eplerenone	Combination therapy with thiazide therapy complicated by hypokalemia. Avoid with kidney disease (eGFR <45 mL/min)	Hyperkalemia, gastrointestinal side effects
Aldosterone antagonists	Spironolactone Triamterene	Preferred therapy for primary aldosteronism and resistant hypertension.	Painful gynecomastia, hyperkalemia, gastrointestinal discomfort, erectile dysfunction, irregular menses
Renin inhibitor	Aliskiren	May cause acute kidney failure with severe bilateral renal artery stenosis. Avoid with ACE inhibitors and/or ARBs and in pregnancy.	Angioedema, hyperkalemia, gastrointestinal discomfort, and can cause acute renal failure in patients with severe bilateral RAS
Vasodilators	Hydralazine Minoxidil	Resistant hypertension	Fluid retention, reflex tachycardia

<sup>a</sup>Preferred because of trial proven in heart failure and stroke prevention and prolonged half-life.

<sup>b</sup>Selective, alpha-1 blockers.

<sup>c</sup>Cardioselective beta blockers.

<sup>d</sup>Preferred in patients with heart failure with reduced ejection fraction.

<sup>e</sup>Noncardioselective beta blockers.

ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; CVD, cardiovascular disease; CYP, cytochrome P450.  
Reprinted with permission. *Hypertension*. 2018;71:e13–e115 ©2018 American Heart Association, Inc.<sup>1</sup>

also be beneficial in patients with osteoporosis. In patients with impaired renal function, thiazide diuretics are generally not effective (serum creatinine >1.5 mg/dL) and loop diuretics are preferred. Lastly, the efficacy of thiazide diuretics is reduced in the setting of excessive dietary sodium intake as well as non-steroidal anti-inflammatory drug use. Overall, thiazide diuretics are effective in lowering BP, should be considered first-line pharmacotherapy, and appear to reduce CVD above other first-line classes (i.e., CCBs, ACE inhibitors, and ARBs).

### Complications/Side effects

Thiazide diuretics must be used with caution as they can lead to electrolyte abnormalities and dose-dependent hypokalemia. In addition, thiazide diuretics should be used cautiously in elderly patients as they may cause volume depletion and in patients with RAS.

### Angiotensin-Converting Enzyme Inhibitors

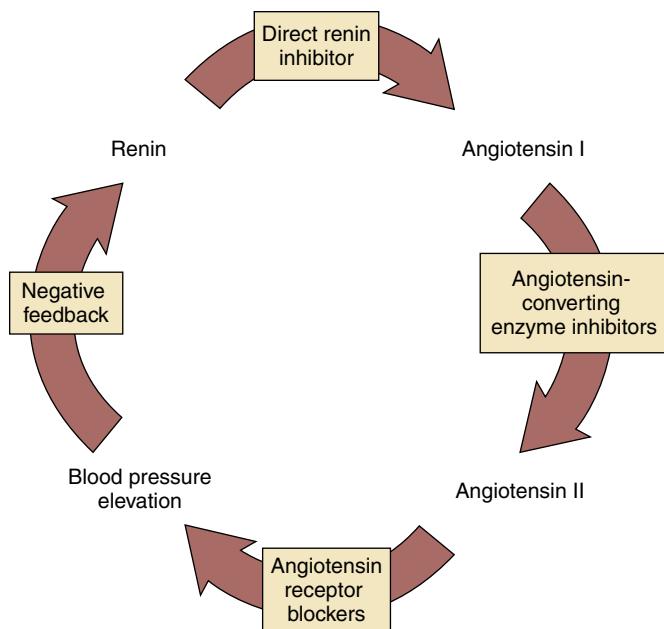
ACE inhibitors block the enzyme that is responsible for converting angiotensin I to angiotensin II (Fig. 14.2). As previously discussed, angiotensin II is a potent vasoconstrictor.

ACE inhibitors work synergistically with thiazide diuretics. In addition to lowering BP, ACE inhibitors have been shown to improve endothelial dysfunction and vascular remodeling.<sup>57</sup> Multiple large trials and meta-analysis have demonstrated

superiority for ACE inhibitors in patients with PAD and hypertension.<sup>8,48,49</sup> In the Heart Outcomes Prevention Evaluation (HOPE) study, patients with atherosclerotic vascular disease or diabetes treated with ramipril, an ACE inhibitor, had a reduction in acute myocardial infarction, stroke, and all-cause mortality as compared with those randomized to placebo.<sup>62</sup> Two large meta-analyses, including nearly 100,000 total patients, indicated that ACE inhibitors may reduce the recurrence of atrial fibrillation in hypertensive patients with and without heart failure.<sup>1,63,64</sup> In nondiabetic patients with chronic kidney disease and proteinuria, ACE inhibitors decrease mortality and possibly CVD events.<sup>58,65</sup> ACE inhibitors reduce cardiovascular morbidity and mortality but may be inferior to CCBs and thiazide diuretics in the prevention of stroke and heart failure in Black patients without specific comorbidities.<sup>54,55</sup> Therefore, this class can be considered standard first-line pharmacotherapy and recommended as initial pharmacotherapy among patients with proteinuria and diabetes or chronic kidney disease, in whom thiazides are minimally effective.<sup>1</sup>

### Complications/Side effects

A common side effect of ACE inhibitors is a dry cough, which is thought to be bradykinin mediated. ACE inhibitors are also associated with the rare, but potentially life-threatening, side effect of angioedema. Due to the common



**Figure 14.2** Site of action of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and direct renin inhibitors within the renin–angiotensin system.

co-existence of RAS in patients with PAD, the initiation of ACE inhibitors must be done cautiously in this population to avoid acute kidney injury.<sup>66</sup> Hyperkalemia may also result from ACE inhibitor pharmacotherapy, especially in patients with impaired renal function. Lastly, ACE inhibitors are contraindicated in pregnancy due to increased risk of cardiovascular and central nervous system congenital malformations.<sup>67</sup>

### Angiotensin Receptor Blockers

Angiotensin II binds to the AT1 receptor, which triggers vasoconstriction. ARBs work by inhibiting the AT1 receptor. ARBs have similar indications and benefits as ACE inhibitors in regard to patient comorbidities. In the Losartan Intervention for Endpoint (LIFE) trial patients with hypertension and left ventricular hypertrophy treated with losartan had a lower incidence of CVD morbidity and mortality as compared with patients treated with atenolol.<sup>68</sup> The ONTARGET trial evaluated the ARB telmisartan in comparison to ramipril. Patients treated with telmisartan had equivalent cardiovascular outcomes with a lower risk of angioedema.<sup>69</sup> The combination of ACE inhibitors and ARBs was also evaluated in ONTARGET and other studies, and was associated with an increased risk of adverse events without additional clinical benefit.<sup>69,70</sup> In general, ARBs are noninferior to ACE inhibitors, are better tolerated due to lower incidence of cough, and have a lower overall risk of hyperkalemia and angioedema. Like ACE inhibitors, ARBs are considered standard first-line pharmacotherapy, may be inferior to CCBs and thiazide diuretics in heart failure and stroke prevention in all comers, but are recommended as first-line pharmacotherapy among patients with proteinuria and diabetes or chronic kidney disease and may reduce the recurrence of atrial fibrillation.<sup>1,63,64</sup>

### Complications/Side Effects

Similarly to ACE inhibitors, ARBs have a risk of congenital malformations and are contraindicated during pregnancy.<sup>67</sup>

### Calcium Channel Blockers

CCBs work by interacting with the L-type voltage gated plasma membrane calcium channels to disrupt calcium transport. CCBs are subdivided into two groups: the dihydropyridines and the non-dihydropyridines. The dihydropyridines are potent vasodilators and increase salt excretion and may be effective in patients who are unable to adhere to salt-restricted diets or those taking nonsteriodals (in whom thiazide diuretics would be less effective). The non-dihydropyridines are negative chronotropic and inotropic agents and should not be prescribed to patients with heart failure and a reduced ejection fraction. There is some evidence that CCBs may benefit patients with claudication.<sup>71</sup> However, clinical guidelines do not support the use of CCBs as treatment for claudication nor have CCBs been found to be superior in PAD.<sup>8,48,49</sup> As described above, evidence suggests CCBs are likely equivalent to thiazide diuretics, but superior to ACE inhibitors and ARBs in the prevention of stroke and heart failure.<sup>1</sup> Women with hypertension who are planning to become pregnant can be transitioned to nifedipine.

### Complications/Side effects

CCBs, specifically the non-dihydropyridines, must be used with caution in patients with underlying cardiac conduction abnormalities as they will lower the heart rate. In patients with heart failure with reduced ejection fraction, non-dihydropyridines CCBs should be avoided as they provide no functional or CVD event benefit and may confer an increased risk of death. In addition, the dihydropyridines may cause lower extremity edema which can be managed in combination with a diuretic.

### Beta Blockers

Beta blockers inhibit beta-adrenergic receptors. There are different categories of beta blockers, including nonselective, cardioselective, and those with alpha blocking properties. Beta blockers were previously considered first-line pharmacotherapy for primary hypertension. However, several meta-analyses have shown beta blockers are inferior for preventing CVD events in patients without prior ischemic heart disease.<sup>57,72</sup> Beta blockers are indicated for patients with coexisting comorbidities including coronary artery disease and heart failure.

### Complications/Side effects

Beta blockers may cause fatigue, predispose patients to depression, and reduce exercise tolerance. Beta blockers also antagonize the bronchial beta receptors that mediate bronchodilation and may be poorly tolerated in patients with asthma or severe chronic obstructive pulmonary disease. Beta blockers should be used cautiously in patients with cardiac conduction abnormalities. Previously, beta blockers were thought to be contraindicated in PAD due to the risk of exacerbating peripheral vasoconstriction; however, there is now evidence that beta blockers are safe in PAD.<sup>73</sup>

## **Loop Diuretics**

Loop diuretics work in the thick ascending limb of the loop of Henle by blocking the reabsorption of sodium, chloride, and potassium. Because of their effectiveness at blocking sodium and water reabsorption, loop diuretics are particularly useful in patients in states of salt and volume excess (e.g., heart failure, renal failure). Generally, loop diuretics are less potent antihypertensives than thiazide diuretics but they cause fewer metabolic derangements.

### **Complications/Side effects**

Loop diuretics can lead to volume depletion and electrolyte abnormalities (specifically, hypokalemia) and are associated with allergic reactions, especially in patients allergic to sulfa.

## **Potassium-Sparing Diuretics**

The potassium-sparing diuretics work in the distal convoluted tubule or collecting tubule, where they block the reabsorption of sodium without blocking potassium reabsorption. This class of medications is minimally effective at reducing BP as monotherapy and they are often used as an adjunct to prevent diuretic-related hypokalemia.

### **Complications/Side effects**

These drugs should be avoided in the setting of kidney disease. Triamterene acts as a folate antagonist and is contraindicated in pregnancy.

## **Aldosterone Receptor Antagonists**

Aldosterone receptor antagonists are effective at treating hypertension associated with aldosterone excess in the setting of primary aldosteronism. Eplerenone is more selective and has less impact on androgen and progesterone.

### **Complications/Side effects**

Both medications are associated with hyperkalemia and patients with chronic kidney disease should be carefully monitored.

## **Alpha Blockers**

Alpha blockers target the alpha-adrenergic receptors. The use of these medications has decreased over time, particularly after the ALLHAT study showed an increased risk of heart failure in patients treated with the alpha blocker doxazosin.<sup>53</sup> The alpha-1 blockers are useful in men with benign prostatic hypertrophy, as they have smooth-muscle relaxation properties and can relieve lower urinary tract obstructive symptoms. Nonselective alpha antagonists are used primarily in the management of pheochromocytomas.

### **Complications/Side effects**

The alpha blockers are associated with dizziness, orthostatic hypotension (especially in older adults), fatigue, nasal congestion, and headache.

## **Centrally Acting Alpha Antagonists**

The centrally acting alpha antagonists, clonidine (oral or patch administration) and methyldopa, work to lower BP by

inhibiting sympathetic activity. Clonidine can be administered transdermally, which has the benefits of continuous drug delivery, reduced side effects, and improved adherence. Methyldopa is safe to use in pregnancy.

### **Complications/Side effects**

Although effective, clonidine is considered fourth-line pharmacotherapy because of the potential for rebound hypertension and other side effects. Methyldopa also may cause orthostatic hypotension, fluid retention, hepatotoxicity, and hemolytic anemia.

## **Direct Vasodilators**

Vasodilators are a fourth-line agent used in patients with resistant hypertension. Hydralazine is commonly used in conjunction with nitrates for afterload reduction in patients with heart failure with reduced ejection fraction. It is combined with isosorbide dinitrate in an approved fixed-dose combination drug BiDil which is indicated in Black patients with systolic heart failure.<sup>74</sup> Minoxidil is generally used only in patients with resistant hypertension and impaired renal function.

### **Complications/Side effects**

Hydralazine may cause drug-induced lupus-like syndromes at higher doses. Minoxidil is associated with fluid retention requiring concurrent loop diuretic therapy, tachycardia requiring concurrent beta blockers, and hirsutism.

## **Renin Inhibitors**

Aliskiren blocks the first step in the renin–angiotensin–aldosterone system. It is very long acting and has been shown to have equal efficacy as ACE inhibitors, ARBs, and diuretics in reducing BP.<sup>75</sup> Aliskiren is more effective at reducing BP when combined with ACE inhibitors or ARBs than as monotherapy.<sup>76</sup> However, the FDA has cautioned against the use of aliskiren in combination therapy with ACE inhibitors or ARBs due to the results of the Aliskiren trial in type 2 diabetes using cardiovascular endpoints (ALTITUDE) trial that showed a higher rate of cardiovascular and renal adverse events and hyperkalemia in patients treated with combination therapy.<sup>77,78</sup>

### **Complications/Side effects**

Given the side-effect profile of this medication, it is not commonly used.

## **Emerging Therapies**

### **Experimental Invasive Therapies**

In addition to lifestyle modifications and antihypertensive pharmacotherapy for hypertension, new technologies are currently being evaluated, especially for resistant hypertension.

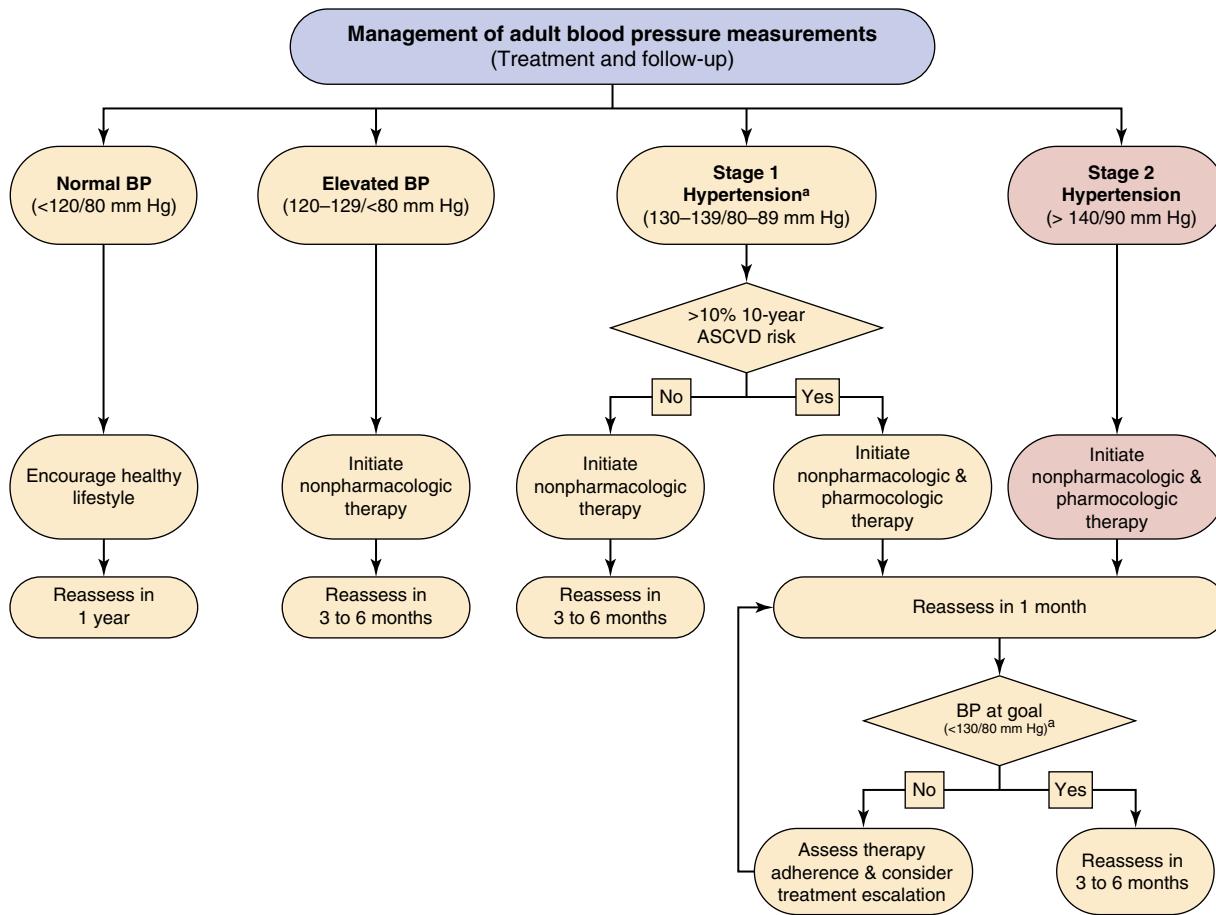
The carotid sinus baroreceptors play an important role in BP regulation. Stimulation of the carotid sinus via an implanted device has been investigated as a treatment for patients with resistant hypertension. The first generation of carotid sinus simulators, the Rheos device, included a surgically implanted pulse generator, bilateral carotid leads, and a programmer system.<sup>79,80</sup>

The Phase III Rheos Pivotal Trial was a double-blind, randomized, placebo-controlled trial<sup>80</sup> which showed a significant benefit of the Rheos device with regards to efficacy. However, the trial did not meet the endpoints for acute responders or procedural safety due to facial nerve injury.<sup>81</sup> The trial was deemed equivocal and usage of this technology has been limited.<sup>82</sup> A second-generation, smaller carotid sinus baroreceptor activation system is under evaluation, the Neos system. The BAROSTIM THERAPY prospective, observational trial is recruiting 500 patients, monitoring BP, pharmacotherapy changes, and hospitalizations for 3 years of follow-up.<sup>83</sup> This and future trials are needed to evaluate the safety of and indication for carotid baroreceptor therapy in resistant hypertension.

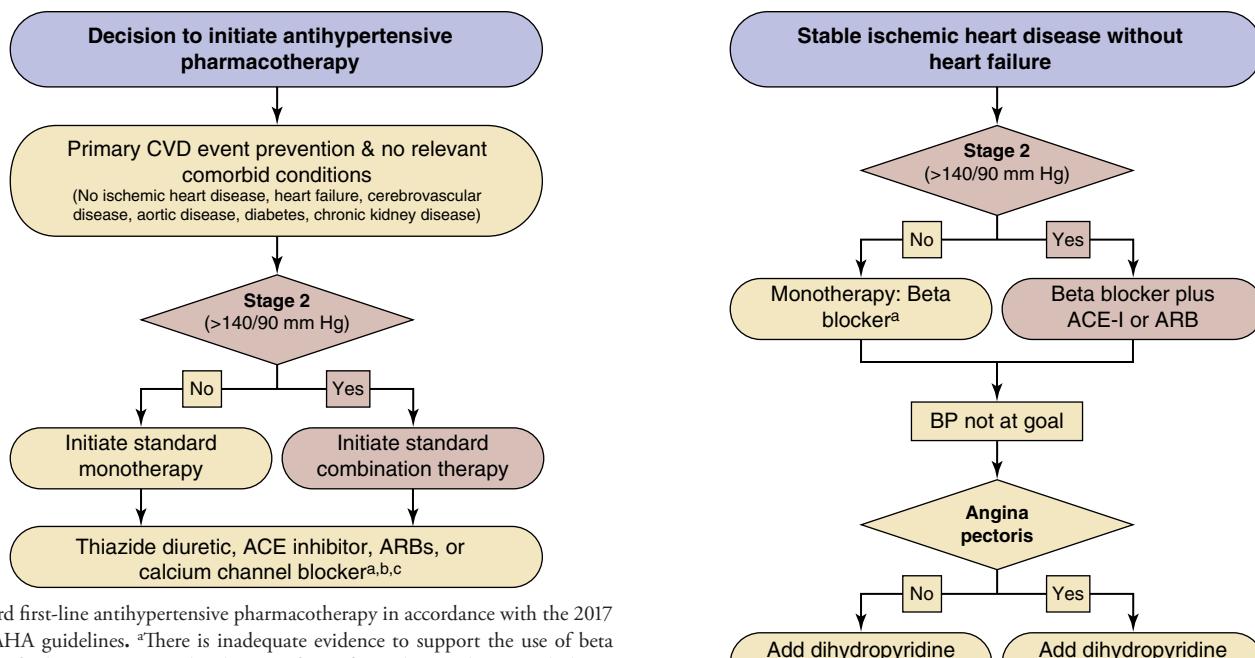
In patients with resistant hypertension, increased sympathetic activity is present and can be difficult to treat pharmacologically.<sup>84</sup> From this came the idea that sympathetic renal innervation could be interrupted to decrease sympathetic activity as a treatment for hypertension. Renal denervation is

a minimally invasive, catheter-based procedure that uses radiofrequency pulses in the adventitial layers of the renal arteries to ablate the nerves in the vascular wall to reduce sympathetic tone. Renal denervation decreases renal sympathetic afferent and efferent activity, which indirectly reduces BP<sup>85</sup>. The initial clinical trials evaluating catheter-based renal denervation, SYMPLICITY HTN-1 and -2, showed significant and sustained reductions in BP by as much as 33 mm Hg at 3 years.<sup>85,86</sup> Other larger trials failed to demonstrate a benefit of denervation to medical management with (SYMPLICITY HTN-3)<sup>87</sup> and without a sham (SYMPATHY).<sup>88,89</sup> The explanation for the significant discrepancy between the first two SYMPLICITY trials and later trials is not clear, but some have surmised that the extent of renal denervation may have not been adequate or consistent.<sup>90</sup> Consequently, the ACC/AHA conclude there is insufficient evidence to recommend this procedure and new technologies are currently being developed to improve renal denervation.

## CHAPTER ALGORITHMS

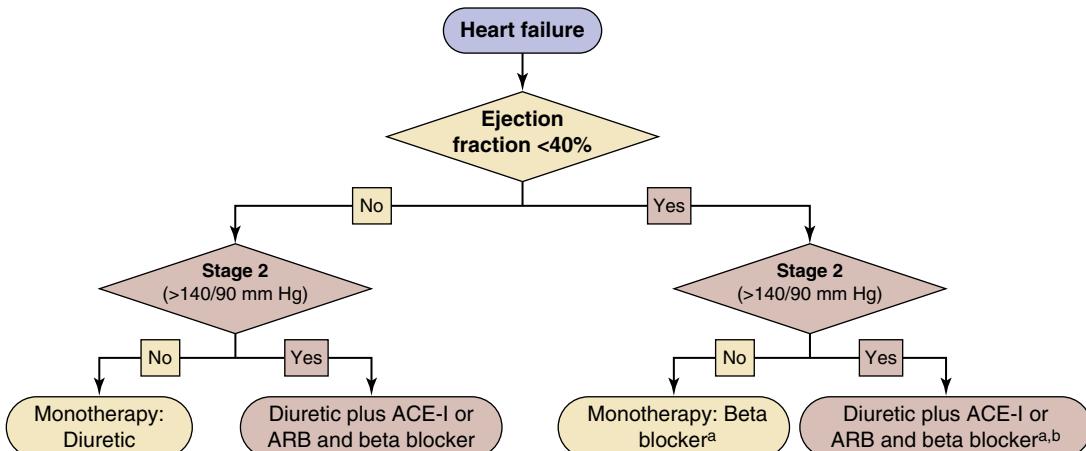


Management of blood pressure measurements in accordance with the 2017 ACC/AHA guidelines. <sup>a</sup>A lower BP target (<130 mm Hg) may be beneficial, especially among those at high risk of CVD events. ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure.



Standard first-line antihypertensive pharmacotherapy in accordance with the 2017 ACC/AHA guidelines. <sup>a</sup>There is inadequate evidence to support the use of beta blockers for hypertension in the absence of specific cardiovascular comorbidities. <sup>b</sup>Calcium channel blockers and thiazide diuretics provide superior heart failure and stroke prevention in Black patients and should be first-line therapy. <sup>c</sup>Long-acting thiazide diuretics may be the optimal first-line antihypertensive pharmacotherapy. ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; CVD, atherosclerotic cardiovascular disease.

First-line therapy in patients with stable ischemic heart disease in accordance with the 2017 ACC/AHA guidelines. <sup>a</sup>Goal-directed medical management beta blockers include carvedilol, metoprolol succinate, or bisoprolol. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCBs, calcium channel blockers.



First-line therapy in patients with heart failure in accordance with the 2017 ACC/AHA guidelines. <sup>a</sup>Goal-directed medical management beta blockers include carvedilol, metoprolol succinate, or bisoprolol. <sup>b</sup>Non-dihydropyridine CCBs are not recommended for patients with reduced ejection fraction. ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

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*A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com).*

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# Familial Arteriosclerosis

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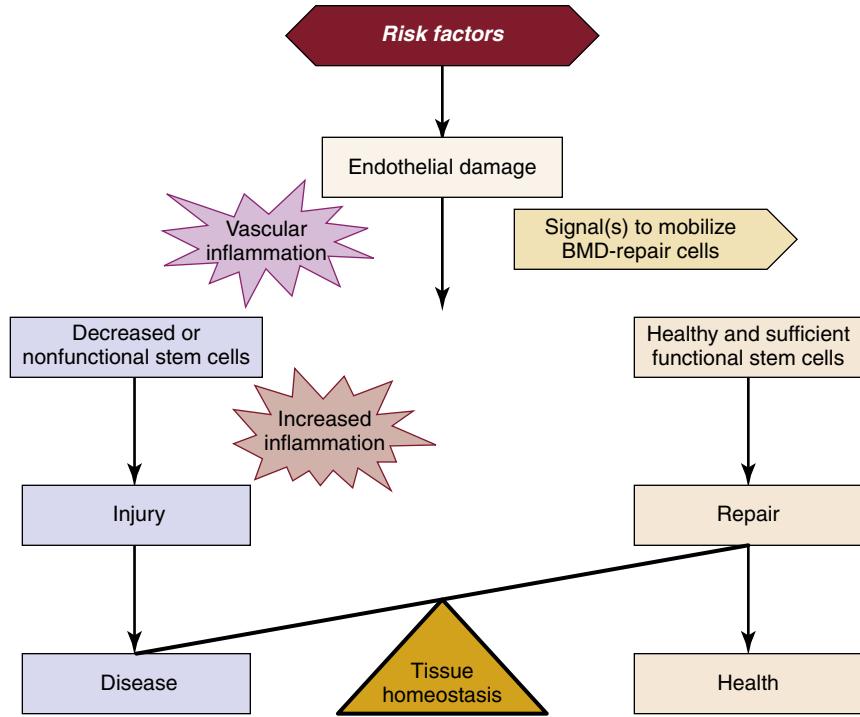
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Atherosclerosis is a disease in which plaque builds up inside of the artery wall, causing the thickening and narrowing of arteries, thereby reducing blood supply to the end organs. Plaque is made up of fatty substances, cholesterol, cellular waste products and debris, calcium, fibrin, inflammatory cells, and platelets.<sup>1,2</sup> It can affect any artery in the body, including arteries in the heart, brain, kidneys, and legs.

Atherosclerosis is the result of nonresolving interactions of inflammation, oxidative stress, lipid deposition, and genetic predisposition.<sup>3</sup> In addition, a novel concept for atherosclerosis risk implicates a lack of endothelial progenitor cell (EPC)-dependent arterial repair in the development of the disease, secondary to the exhaustion of repair-competent EPCs. Molecular evidence derived from genetic techniques indicates that atherosclerotic lesions may begin to form as arterial repair fails, rather than merely following arterial injury. Thus, chronic arterial injury may overwhelm the ability of EPCs and other vascular progenitor cells to maintain arterial homeostasis, particularly when EPCs capable of arterial repair become exhausted. Imbalance between arterial damage and repair leads to atherosclerosis (Fig. 15.1).<sup>4,5</sup>

Cholesterol is a fat-like substance used by cells to synthesize hormones, vitamin D, and substances that help with food digestion. However, elevated plasma cholesterol levels build up within the arterial walls and increase the risk of atherosclerosis. All nucleated cells can synthesize the enzymes to produce cholesterol, and the rate-limiting enzyme in this pathway is

3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. The product of HMG-CoA reductase, mevalonic acid, appears in plasma and urine and may be used as a guide to cholesterol synthetic activity. Post-synthesis, cholesterol is then transported in the bloodstream in small packages called *lipoproteins*. There are two main kinds of lipoproteins: low-density (LDL) and high-density lipoprotein (HDL). HDL carries cholesterol from other parts of the body to the liver, where it is removed from the body. Higher levels of HDL lower a person's chances for getting CAD. LDL carries cholesterol to cells with LDL receptor (LDLR), which are then internalized and degraded. However, patients with familial hypercholesterolemia (FH) have high levels of plasma LDL due to loss of function mutations that result in an inability to remove the LDL from the bloodstream. Atherosclerosis is ultimately a universal disease of aging, with compounding additional risk factors. Of the major genetic risk factors, family history is the most significant independent one.<sup>6–8</sup> FH, familial hypertension, familial diabetes, and familial obesity are at the top of the list of heritable and genetic risk factors. Moreover, these multiple heritable and genetic risk factors can cluster, in many cases, in families. Although FH is the best-characterized heritable risk factor in familial arteriosclerosis, it explains only a small percentage of disease susceptibility. Most of the clinical atherosclerotic diseases result from the interactions of multiple genetic and environmental factors, none of which usually can cause disease by itself.



**Figure 15.1** Imbalance Between Arterial Damage and Repair Leads to Atherosclerosis. Dysfunction of bone marrow-derived (BMD) stem cells or EPC-dependent arterial repair likely tips the balance toward the development of atherosclerosis.

## FAMILIAL HYPERCHOLESTEROLEMIA

FH is a monogenic dyslipidemia characterized by an accumulation of low-density lipoprotein (LDL) in the plasma that results in severe hypercholesterolemia with variable expression of pathognomonic traits such as: tendinous xanthomas, arcus cornea, and xanthelasma. Eventually FH patients develop precocious atherosclerotic cardiovascular disease (ASCVD) events such as myocardial infarction, stroke, and limb ischemia.<sup>9</sup>

FH is an autosomal dominant disease caused by mutations in the genes encoding the *LDL receptor* (*LDLR*), which normally removes LDL from the circulation; apolipoprotein B (ApoB), which is the part of LDL that binds with the receptor; or proprotein convertase subtilisin/kexin type 9 (*PCSK9*), which induces degradation of *LDLR*; and the adaptor protein, or autosomal recessive hypercholesterolemia (ARH) protein (*LDLRAP*), which facilitates the clearance of circulating LDL (Fig. 15.2).<sup>10</sup> Mutations in these genes result in loss of function of these molecules and contribute to elevated plasma levels of LDL. People who have one abnormal copy (are *heterozygous*) in one of three genes (*LDLR*, *ApoB*, *PCSK9*) may have premature CAD at the age of 30 to 40. Having two abnormal copies (being *homozygous*), either biallelic pathogenic variants in one of these known genes or one pathogenic variant in each of two different genes, may result in severe CAD in childhood.<sup>10</sup>

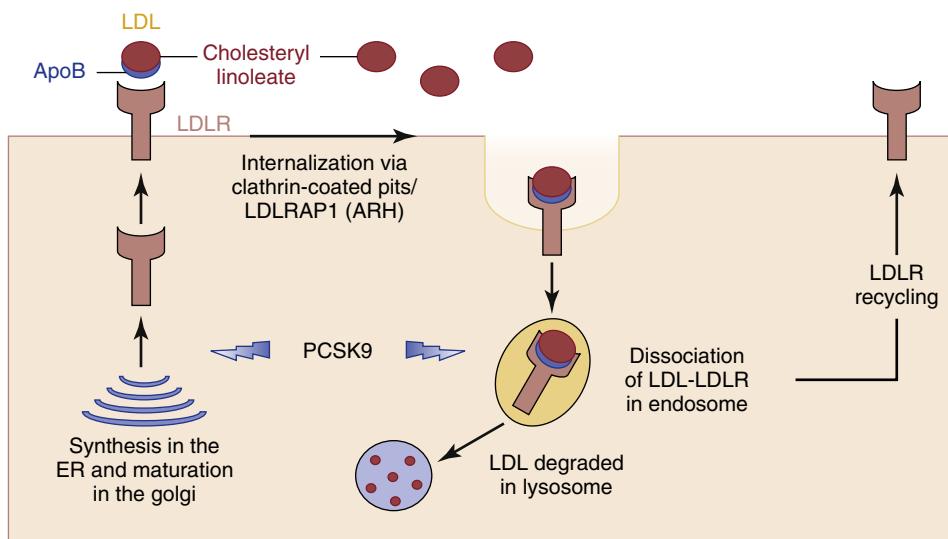
Heterozygous FH (HeFH) is more common and accounts for 60% to 80% of FH, with a prevalence estimated at 1 per 200 to 500 of persons with FH. Persons with untreated FH are at an approximately 20-fold increased risk for CAD. Untreated men are at a 50% risk for a fatal or nonfatal coronary event by age 50 years; untreated women are at a 30% risk by age 60 years. In contrast, homozygous FH (HoFH) is incredibly rare

with a prevalence of about 1 per 160,000 to 1 million. Most individuals with HoFH experience severe CAD by their mid-20s. The rate of death or coronary bypass surgery by adolescence is high. Severe aortic stenosis is also common.<sup>11,12</sup>

As previously discussed, several mutations in genes regulating LDL homeostasis result in FH. One such mutation is the LDLR, a well-characterized cell surface transmembrane protein that binds LDL,<sup>13</sup> which then becomes internalized as a complex. Once in the endosome, the LDLR dissociates from the lipoprotein during acidification while the LDL proceeds to the lysosome for enzymic degradation into its constituent cholesterol, fatty acids, and amino acids. The dissociated LDLR can be retransported back to the cell surface and recycles approximately 150 times before degradation.<sup>14</sup>

The defect of LDLR results in accumulation of LDL in the bloodstream, leading to FH. Numerous defects in the LDLR have been divided into six classes, depending on the impact of the mutation on the presence of mRNA, receptor maturation in cells, disparity between LDL and immunoglobulin binding on the cell surface, and LDLR degradation and trafficking.<sup>15</sup> These LDLR classes of mutations affected the synthesis, cellular transport, ligand binding capacity, ability to internalize, recycle, and localize to the basolateral membrane (Table 15.1). Although defective hepatic LDL uptake is the main and most direct consequence, other metabolic perturbations may contribute to the metabolic characteristics and accelerated atherosclerotic disease associated with FH.

The defective apoB100 is another common reason for FH. Compared with the numerous mutations found in the LDLR and its pathway, very few mutations have been reported in apoB100 that result in disruption of ligand binding of LDL to the LDLR. Individuals with heterozygous familial binding



**Figure 15.2** The LDL-Receptor Pathway for Uptake and Degradation of LDL. The LDL receptor is a cell-surface glycoprotein that is synthesized as an immature protein and processed in the Golgi apparatus, producing the mature form that is transported to the cell surface. There, the receptor specifically binds apoB in LDL particles present in the extracellular fluid. The receptor-ligand complex is then internalized by endocytosis via clathrin-coated pits through interactions involving LDLRAP1 (ARH). The complex is transported via early endosomes to the late endosomal compartment, where the acidic environment causes dissociation of the receptor-ligand complex. The receptor is recycled to the cell surface while the LDL particle is degraded in the lysosomal compartment. Accumulation of free cholesterol released by hydrolysis of cholestrylin esters in the core of LDL inactivates sterol regulatory element binding protein (SREBP), a transcription factor that drives expression of genes for enzymes involved in cholesterol synthesis and the LDL receptor. Thus the LDL-receptor pathway maintains intracellular cholesterol homeostasis. The PCSK9 normally reduces the LDL-protein content of cells by a post-translational mechanism that is not yet fully understood. Mutations in *LDLR*, *ApoB*, *LDLRAP1*, or *PCSK9* are known to result in FH. *ApoB*, apolipoprotein B; *ARH*, autosomal recessive hypercholesterolemia; *FH*, familial hypercholesterolemia; *LDL*, low-density lipoprotein; *LDLRAP1*, low-density lipoprotein receptor 1; *PCSK9*, proprotein convertase subtilisin/kexin type 9.

**TABLE 15.1** LDLR Mutation Classification System

Class	Functional Defect
1	Largely due to promoter mutations, leave no detectable mRNA and no detectable LDLR synthesis
2	Absent (Class 2A) or impaired (Class 2B) maturation of LDLR protein
3	Normal LDLR synthesis, however impaired LDL binding due to mutations in the binding domain of LDLR
4	LDLR mature normally and can bind LDL; however, cannot cluster in coated pits on cell surface and thus are unable to internalize upon ligand binding
5	LDLR receptors have inability to recycle and are rapidly degraded
6	Failure of directing LDLR to basolateral membrane in polarized cells

Adapted from Gidding SS, Champagne MA, de Ferranti SD, et al. The Agenda for Familial Hypercholesterolemia: A Scientific Statement From the American Heart Association [published correction appears in *Circulation*. 2015;132(25):e397]. *Circulation*. 2015;132(22):2167–2192.

defective apoB100 (FDB) exhibit cholesterol levels of about 300 mg/dL due to defective LDL clearance.<sup>3</sup> In homozygous FDB, there appears to be no significant gene dose effect.<sup>16</sup> Two homozygotes for FDB were reported to have cholesterol concentrations in the range of heterozygotes for LDLR mutations.<sup>17</sup> The binding affinity for LDLR of very low density

lipoprotein (VLDL) was normal in these subjects, whereas LDL affinity was 10% of normal.

An alternative mechanism for FH is mutations in the *PCSK9*<sup>18</sup> gene, which have been known to cause autosomal dominant hypercholesterolemia.<sup>18</sup> This gain of function mutation increases the affinity of the PCSK9 protein for the LDLR, which results in diminished LDL-LDLR complex dissociation in exosomes, decreased LDLR recycling and increased LDLR degradation, all together resulting in fewer LDLR available on the cell-surface for LDL plasma clearance, thus resulting in FH.<sup>19</sup>

The *APOE*<sup>20,21</sup> gene is another location for potential FH mutations. Mutations in ARH, the adaptor protein, can impair the internalization of LDLR and thus LDL plasma clearance.<sup>20,21</sup> This particular type of FH is a rare, autosomal recessive variant that is less severe than the LDLR mutations seen in more common HoFH phenotype.<sup>22</sup>

While FH, as a monogenic dyslipidemia, results in large increases in LDL levels, the variations in the clinical presentation cannot altogether be explained by their distinct mutations. Thus there are likely other genes acting on LDL levels. Whole exome sequencing studies have demonstrated that single nucleotide polymorphisms (SNPs) can also affect LDL levels.<sup>23</sup>

## FAMILIAL HYPERTENSION

Hypertension is a well-known risk factor for atherosclerosis.<sup>24</sup> Over time, excessive pressure can damage the arteries, making

them more vulnerable to the continued inflammation that results in plaque build-up associated with atherosclerosis. Hypertension tends to be familial and is likely to be the consequence of an interaction between genetic and environmental factors. About 30% to 50% of the variance in blood pressure readings is attributable to genetic heritability and about 50% to environmental factors.<sup>25</sup> The heritability of blood pressure frequently ranges about 50% to 70% in twins, with considerably lower estimates (around 20% to 25%) in family studies.<sup>26–28</sup> In spite of substantial efforts and progress in elucidating the genetic basis for heritable hypertension, the genetic factors contributing to common forms of hypertension remain largely unknown. The genetics of hypertension is complex, with no known single gene playing a major role but rather many genes, each with mild effects, reacting to different environmental stimuli and thus contributing to elevated blood pressure. Early studies in hypertension identified specific enzymes, channels, and receptors implicating sodium handling in the regulation of blood pressure, including genes involved in the renin–angiotensin–aldosterone system (RAAS), controlling blood pressure and salt-water homeostasis, proteins in hormonal regulation of blood pressure (enzymes and receptors of the mineralo- and glucocorticoid pathways), and proteins coded by genes involved in the structure and/or regulation of vascular tone (endothelins and their receptors).<sup>29</sup> RAAS plays an important role in regulating blood pressure and during hypertensive crises (Fig. 15.3).<sup>30</sup> The enzyme renin acts on angiotensinogen (AGT) to generate angiotensin I (Ang I). Ang I is further converted to angiotensin II (Ang II) by angiotensin-converting enzyme (ACE). Ang II exerts its effects by binding to two major types of receptors – AT1R and AT2R.<sup>31</sup> Functions like vasoconstriction, cellular

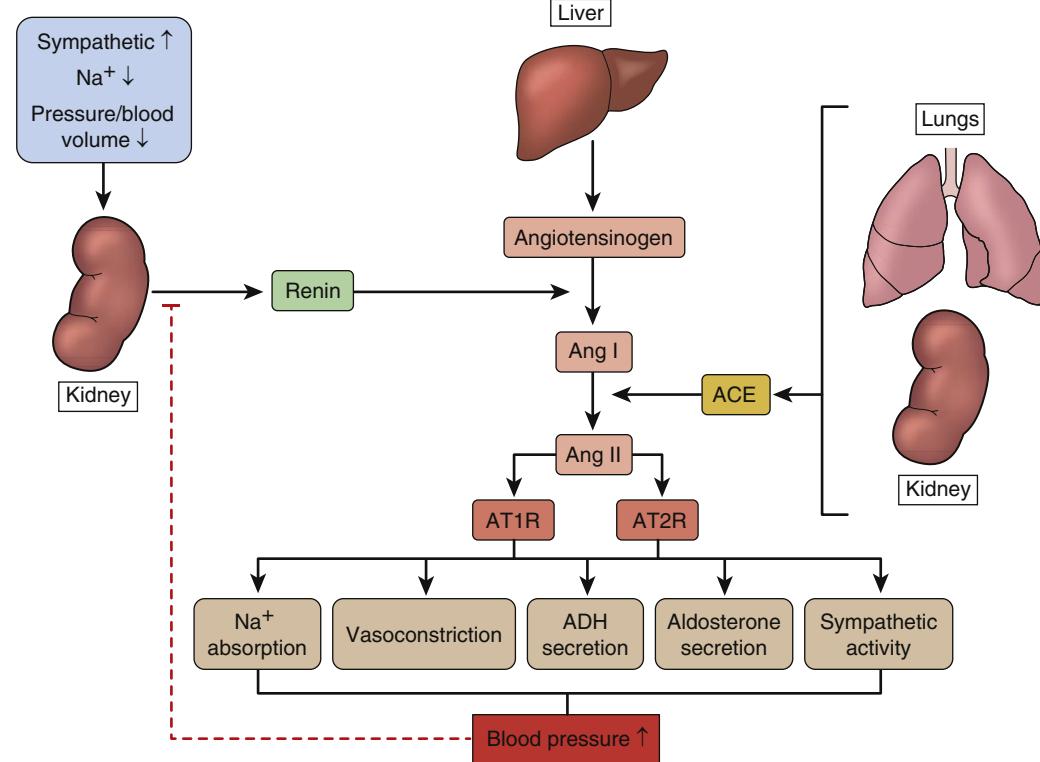
proliferation, cellular hypertrophy, fibrosis, atherosclerosis, antinatriuresis, and the release of aldosterone, endothelin, norepinephrine, and vasopressin are initiated by the binding of Ang II to AT1R. In addition, Ang II directly stimulates vascular smooth muscle cell (SMC) growth and extracellular matrix production. Studies with spontaneously hypertensive rats indicate that raised blood pressure stimulates the expression of platelet-derived growth factor (PDGF), a potent mitogen for SMC.<sup>32</sup> Furthermore, both renin receptors (recently identified) and functionally active Ang II-derived peptides like Ang 1 to Ang 7 have been shown to play pathologic roles in the development of hypertension.<sup>33</sup> Both linkage and association studies have provided strong evidence for the role of the AGT gene in hypertension in Caucasian and African/Caribbean populations as well as in pregnancy-induced hypertension.<sup>34</sup>

The kidney is known to be the dominant, long-term regulator of blood pressure,<sup>35–37</sup> highlighting the need for an appreciation of its pathophysiology in considering genetic factors potentially contributing to hypertension. Moreover, pheochromocytoma is a rare cause of hypertension that may be familial.

## FAMILIAL DIABETES

Cardiovascular disease (CVD) is more prevalent in type 1 and type 2 diabetes (T1D and T2D) and continues to be the leading cause of death among adults with diabetes. T2D, commonly referred to as insulin resistance, is partly inherited.<sup>38</sup>

Insulin resistance is also associated with the enhanced generation of reactive oxygen species (ROS). In addition, insulin resistance decreases NO production,<sup>39–41</sup> and increases the release of free fatty acids from adipose tissue. Increased circulating



**Figure 15.3** Renin–Angiotensin–Aldosterone System (RAAS). When renin is released into the blood, it acts upon angiotensinogen, which undergoes proteolytic cleavage to form Ang I. Vascular endothelium, particularly in the lung and kidney, produces ACE, which cleaves off two amino acids to form Ang II. Ang II binds with AT1R and AT2R to exert its effect on increasing blood pressure. High blood pressure inhibits renin production by kidney. ACE, angiotensin-converting enzyme; Ang I, angiotensin I.

levels of free fatty acids may impair endothelial function<sup>40–42</sup> and induce low-grade inflammation.<sup>41,42</sup> Hyperinsulinemia augments VLDL synthesis in liver; increases cholesterol transport/synthesis in cultured arterial SMCs; stimulates the proliferation of arterial SMCs; augments collagen synthesis and turns on multiple genes involved in inflammation.<sup>43,44</sup> Although insulin receptors are expressed on endothelial cells, vascular SMCs, and macrophages, it remains unclear whether the vascular insulin receptors contribute directly to the vascular pathology of metabolic insulin resistance.<sup>45</sup>

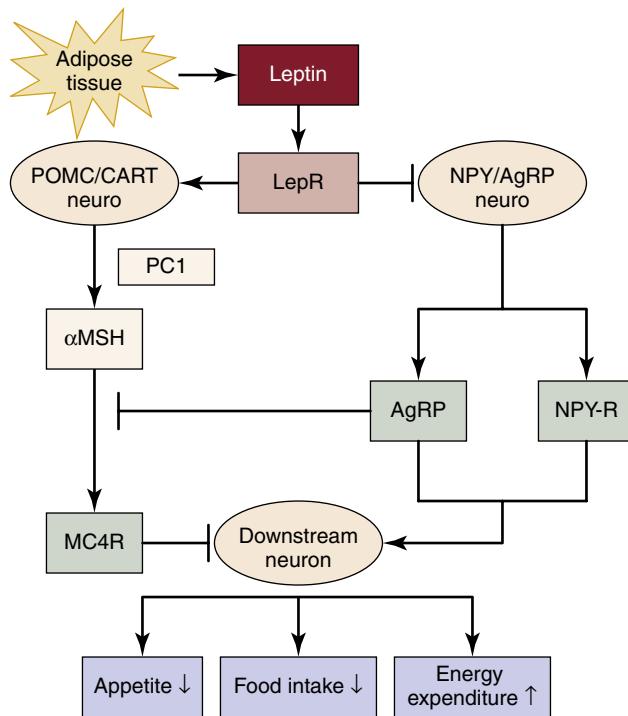
A subset of insulin-resistant individuals develop non-insulin-dependent diabetes mellitus (NIDDM), characterized by an insufficient insulin secretory capacity to maintain normal glucose levels. A genome scan identifies a major NIDDM susceptibility locus, designated NIDDM1, on chromosome 2q. Using linkage disequilibrium mapping, scientists have shown that an intronic polymorphism in the calpain-10 gene is strongly associated with the disease.<sup>46</sup> A second locus for diabetes has been identified on chromosome 1q.<sup>47–50</sup> It is interesting to note that the chromosome 1 locus was initially linked with familial combined hyperlipidemia (FCH) in a set of Finnish families, and that FCH overlaps with diabetes.<sup>51</sup>

Advances in genotyping technology have facilitated rapid progress in large-scale genetic studies. Genome-wide associated studies (GWAS) and linkage analyses have identified greater than 120 genetic variants associated with T2D and diabetes-related traits.<sup>52–55</sup> Most of these variants are noncoding variants; therefore, their functional consequences are challenging to investigate. However, many of the variants identified to date regulate insulin secretion and not insulin action in insulin-sensitive tissues.

## FAMILIAL OBESITY

Although some studies have suggested that obesity is not an important contributing cause of atherosclerosis and CAD,<sup>56,57</sup> recent evidence indicates that obesity is a major contributor to CVD risk and mortality.<sup>58–60</sup> Obesity exhibits considerable metabolic overlap with the abnormalities present in individuals with T2D and is associated with other cardiovascular factors such as hypertension, hyperlipidemia, and insulin resistance.<sup>61,62</sup>

Obesity is a complex disease resulting from the interaction of a wide variety of hereditary and environmental factors. Clustering of cases within a family, the congruence of body weight in monozygotic twins, and the discovery of genes associated with obesity all suggest genetic involvement in obesity. Obesity risk is 2–8 times higher for a person with a family history as opposed to a person with no family history of obesity, and an even higher risk is observed in cases of severe obesity. Occurrences of monogenic types of obesity are evidence that obesity may be caused by genetic mutations. Eight monogenic genes and four polygenic genes have been associated with obesity.<sup>63</sup> The cloning of the mouse ob gene and its human homologue, leptin,<sup>64</sup> has proved to be a paradigm for the field, resulting in the identification of many genes involved in the regulation of appetite, food intake, and energy expenditure via the leptin-melanocortin pathway (Fig. 15.4). These variants account for



**Figure 15.4** Influence of the Leptin–Melanocortin Pathway on Food Intake and Energy Expenditure. Leptin secreted from adipose tissue binds to the leptin receptor (LepR) in the hypothalamus. Leptin binding inhibits the neuropeptide Y/agouti-related protein (NPY/AgRP) production and stimulates pro-opiomelanocortin (POMC) production, which undergoes posttranslational modifications to produce peptides such as alpha-melanocyte-stimulating hormone (αMSH) via the processing of prohormone convertase 1 (PC1). αMSH binds to melanocortin 4 receptors (MC4R) and induces downstream events of food intake and energy consumption.

some 5% of morbid human obesity and include leptin<sup>65</sup> and its receptor,<sup>66</sup> the α-melanocortin-stimulating hormone receptor (MC4R),<sup>67,68</sup> pro-opiomelanocortin (POMC),<sup>69</sup> and prohormone convertase-1.<sup>70</sup> Moreover, the association of additional genes with obesity has recently been identified by GWAS (*SH2B1*, *KCTD15*, *MTCH2*, *NEGR1*, and *BDNF*) with dietary intake and nutrient-specific food preferences.<sup>71</sup> This is in line with the fact that food intake-related parameters are heritable<sup>72</sup> and are strongly correlated with body mass index (BMI).<sup>73</sup>

Other genes such as *fat mass and obesity-associated (FTO)*; *PCSK1*; and *catenin, beta-like 1 (CTNNBL1)* are also associated with obesity. In addition, more than 150 loss-of-function coding mutations have been associated with monogenic obesity,<sup>74</sup> and two infrequent gain-of-function coding polymorphisms (V103I and I251L) have been associated with protection from obesity.<sup>75,76</sup>

## GENETICS OF PERIPHERAL ARTERY DISEASE

PAD is a disease characterized by reduced blood flow to the lower extremities, most often because of atherosclerosis and can be considered a marker of widespread atherosclerosis. However, PAD is a distinct subtype of atherosclerotic vascular

disease that differs from CAD and CVD in its clinical manifestations. Thrombus formation resulting from acute rupture or erosion of a vulnerable plaque in the coronary or cerebral arterial beds leads to acute events such as myocardial infarction (MI) or stroke. Such acute events are relatively uncommon in PAD, and symptoms most often result from progressive arterial narrowing because of ongoing atherogenesis. The underlying reasons for the differences remain unknown. It is therefore likely that risk factors, both genetic and environmental, and the intermediate biochemical pathways through which they act contribute differently to PAD than to CAD or CVD. Although traditional cardiovascular risk factors have been associated with the development of PAD, relatively few genetic variants that influence susceptibility to PAD have been discovered. This may be partly because of the greater clinical and genetic heterogeneity in PAD.<sup>77</sup> Phenotypic heterogeneity seems to be a major challenge in investigating the genetic basis of PAD.

PAD is complex and heterogeneous; it is not a uniform entity. Two broad subtypes of PAD, proximal and distal, are associated with distinct risk factor and comorbidity profiles.<sup>78</sup> Female sex, smoking, hypertension, and dyslipidemia are more significantly associated with proximal disease, whereas older age, male sex, and diabetes are more significantly associated with distal, small vessel disease. The candidate genes include  $\beta$ -fibrinogen,<sup>79</sup> apoB,<sup>80</sup> endothelial nitric oxide synthase (*eNOS*),<sup>81</sup> methylene tetrahydrofolate reductase,<sup>81</sup> *G protein  $\beta$ 3,  $\alpha$ -adducin*,<sup>82</sup> *IL-6*,<sup>83</sup> and glutathione S-transferase.<sup>84</sup> However, any reported associations between variants in these genes and PAD have not been confirmed in independent cohorts or in GWAS. Moreover, genetic analyses do not appear to be as useful as in CAD in determining progression of the disease or its tendency to remain stable.<sup>85</sup>

A linkage analysis using a 10-cM genome-wide scan in 272 PAD patients from 116 extended families has identified a region on chromosome 1 between 100 and 110 cM (logarithm of the odds score, 3.93;  $P = 1.04 \times 10^{-5}$ ) associated with PAD. Several candidate genes (in pathways of inflammation, coagulation, lipid metabolism, blood pressure regulation, and vascular matrix regulation) for atherosclerosis are present under the linkage signals, but the causal variants cannot be identified.<sup>86</sup> Association studies using the GWAS approach identified only a few loci having weaker associations with PAD.<sup>87</sup>

Similar to CAD, several Mendelian disorders are associated with PAD. These include familial lipoprotein disorders, such as chylomicronemia resulting from mutations in the lipoprotein lipase gene and FH,<sup>88,89</sup> hyperhomocysteinemia,<sup>90</sup> and pseudoxanthoma elasticum.<sup>91</sup> In a family history study including 2296 PAD cases and 4390 controls, the prevalence of a family history of PAD was significantly higher among patients with PAD than in controls, resulting in a doubling of the odds of the presence of PAD in those with family history of PAD.<sup>92</sup> The association is stronger in individuals less than 68 years of age and in those with a greater number of affected relatives. In another study conducted in a twin population, the odds ratio of having PAD among individuals whose twins had PAD compared with individuals whose twins did not have PAD was 17.7 for monozygotic twins and 5.7 for dizygotic twins.<sup>93</sup>

## INFLUENCE OF NONGENETIC FACTORS

Although the critical roles of genetic factors in atherosclerotic vascular disease have increasingly been recognized, the specific etiology in many cases remains unknown, with non-genetic risk factors believed to be important contributors. It is now generally considered that atherosclerosis results from a variety of genetic causes, with added epigenetic modulation and the interaction of genetic and environmental factors. None of these triggers is sufficient to cause atherosclerosis on its own.

### Environmental Factors

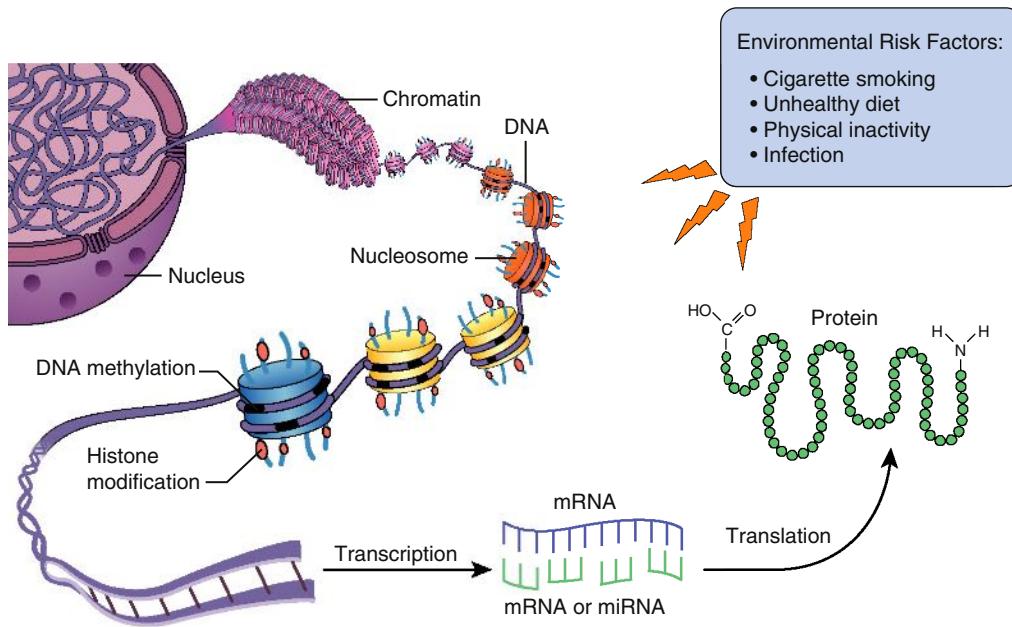
Accumulating evidence strongly supports the existence of gene–environment interactions in atherosclerosis.<sup>94–99</sup> The genetics of atherosclerosis-induced CVDs involves a large number of genes having weak effects on disease risk, but possibly interacting with each other and with environmental factors could act synergistically in the pathogenesis of atherosclerosis and its complications. Gene–environment interactions can be either complementary or antagonistic.<sup>100</sup> Complementary gene–environment interactions may play a substantial role in CAD risk only when an individual with a high-risk genetic profile enters a high-risk environment; that is, the effect on risk will then be so great that premature CAD develops. Indeed, a large number of studies have shown significant gene–environment interactions in the etiology of obesity as well as in the pathogenesis of T2D and CAD.<sup>101–103</sup>

### Epigenetic Factors

Epigenetics plays important roles in the modulation of gene expression and activity. Epigenetics represents a critical link between genomic coding and phenotype expression that is influenced by both underlying genetic and environmental factors. Epigenetic modifications may contribute to subclinical and clinical CAD, CVD, and PAD.<sup>104</sup> *Epigenetics* refers to changes in gene expression resulting from factors other than a direct change in the DNA sequence of the genome. Epigenetic mechanisms for the regulation of gene expression include DNA methylation, posttranslational histone modifications, and posttranscriptional modifications such as small noncoding miRNA (Fig. 15.5).<sup>105</sup> Alteration of gene expression regulated by epigenetics is heritable. Epigenetic inheritance is an essential mechanism that allows the stable propagation of gene activity states from one generation of cells to the next.<sup>106</sup>

## RISK ASSESSMENT AND DIAGNOSIS

The Framingham Risk Score (<https://framinghamheartstudy.org/fhs-risk-functions/hard-coronary-heart-disease-10-year-risk/>) and the ACC/AHA ASCVD Risk Score (<http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#/calculate/estimate/>) are popular tools that guide therapy based on the patient's 10-year risk of ASCVD events, but are not meant to describe heritable



**Figure 15.5** Overview of Gene Expression Regulated by Epigenetic Mechanisms. Histone modifications, DNA methylation, and noncoding (micro) RNAs mediate influence from environment on gene transcription and translation. (Modified from Dr. Clarissa Gerhäuser. Cancer Prevention and Nutrition. *Lab&More Int* 4, 2014.)

**TABLE 15.2** Diagnostic Criteria for Familial Hypercholesterolemia

Family history	Premature CAD (<55 years in men and <60 years in women among first-degree relatives) >95 percentile LDL level for age and gender in first- or second-degree relatives
Clinical history	Patient with premature CAD and/or CVD
Laboratory examination	High LDL levels (>250 mg/L in adult; >200 mg/L in patients <20 years old)
Physical examination	Tendon xanthomas: arcus cornealis
Genetic test	Gene mutation in <i>LDLR</i> , <i>ApoB</i> , or <i>PCSK9</i>
No secondary causes of hyperlipidemia	Normal liver enzymes, renal function, thyroid hormones No hyperglycemia or albuminuria

*ApoB*, apolipoprotein B; *LDL*, low-density lipoprotein; *LDLR*, low-density lipoprotein receptor; *PCSK9*, proprotein convertase subtilisin/kexin type 9

atherosclerosis risk. For patients with genetic susceptibility to CAD, like FH, certain diagnostic algorithms attempt to define one's likelihood of having FH based upon LDL levels, physical findings, and elements of personal and family history. These algorithms include the MedPed Criteria, Simon Broome Register criteria, and Dutch Lipid Clinic Network score<sup>107</sup> (Table 15.2). Recently, Khera et al. described a new classification system for hypercholesterolemia based on (i) monogenetic mutations (as described previously) and/or (ii) presence of  $\text{LDL} \geq 190 \text{ mg/dL}$ . Particularly this new classification designates a category for "Severe Hypercholesterolemia" that lacks a pathogenic FH variant. These patients may have family history of atherosclerosis, which suggests polygenic inheritance, and lack the overt physical findings of FH, however they have a 5-fold increased risk of ASCVD compared to the population without elevated LDL.<sup>107</sup> Thus, the algorithm associated with this chapter utilizes this

methodology for the diagnosis and management of these distinct groups of patients (see Chapter Algorithm).

## Familial Hypercholesterolemia

The diagnosis of both HoFH and HeFH is based primarily on the finding of severe LDL elevations in the absence of secondary causes of hypercholesterolemia (see Table 15.2) and then genetic analysis confirmation of the pathogenic variants. A careful family history is essential for the comprehensive assessment of possible FH in general and HoFH in particular. In the case of autosomal dominant mutations (in *LDLR*, *PCSK9*, and *APOB* genes), both parents are obligate heterozygotes and therefore display elevated LDL levels (frequently >95th percentile) and a strong positive family history of premature CVD (<55 years in men and <60 years in women among first-degree relatives). In the case of *LDLRAP1* mutation-induced ARH, parents may exhibit normal LDL levels, and determination of an extended family pedigree may reveal an autosomal recessive pattern of inheritance.

Definitive diagnosis can be made only with gene or receptor analysis. The genetic diagnosis is popularly made by polymerase chain reaction (PCR) for *LDLR* and *ApoB* defects. Only a few mutations are known in *ApoB*, but there are more than 750 mutations in *LDLR*. New technology, such as next-generation sequencing and RNA-seq, may provide in-depth evaluation for many mutations. These new technologies are currently available in some medical centers for genetic diagnosis. In populations with founder effects, genetic diagnosis is easier. In other populations, where hospitals can sequence the genes in affected families, genetic diagnosis can be made in family members. Moreover, cell culture is more reliable in identifying *LDLR* defects. In fibroblast cultures, *LDLR* mutations will result in low binding, whereas adaptor protein mutations will not. It is worth considering measurement of plasma phytosterols for phytosterolemia and cholestanol for cerebrotendinous

xanthomatosis and investigating the genes influencing the concentration of these products.

Once a definitive diagnosis in the proband is made, systematic cascade or opportunistic screening is recommended. Cascade testing of FH relatives has been given the tier 1 classification by the US Centers for Disease Control and Prevention Office of Public Health Genomics. This testing allows for prenatal counseling for those either homozygous or heterozygous for pathogenic variants, aids in treatment decisions and may influence insurance eligibility for patients that require specific therapies based upon their distinct mutation.<sup>9</sup>

## Familial Hypertension

A family history of hypertension is twice as common in the hypertensive population than in those who are normotensive. As described earlier, a polygenic model of inheritance has been found. Genetic factors include an inherited defect in cellular sodium transport as well as abnormal response to psychogenic stress. Therefore, family history and genetic markers are included in the family hypertension work-up. Other factors to be investigated include T2D, dyslipidemia, BMI, sex, age, smoking, and psychological factors (e.g., stress levels), as multiple factors are more often involved in high-risk CAD associated with family hypertension. Laboratory genetic test may consider *AGT*, which is the first gene to show linkage with human essential or primary hypertension,<sup>108</sup> *ACE*,<sup>109</sup> and *α-adducin (ADD1)*.<sup>110</sup> More information about genetics and hypertension is available at the website of the Centers for Disease Control Office of Public Health Genomics. Currently, genetic testing for primary hypertension is not practical, however certain clinical phenotypes may warrant referral to genetic counselors for consideration of secondary causes of hypertension.<sup>111</sup>

## Familial Diabetes

Family history is increasingly recognized as a powerful, cost-effective, and readily available tool for detecting diabetes. Such information can be used to classify individuals or groups of people according to different levels of familial risk, such as average, moderate, and high.

In most cases of T1D, people must inherit risk factors from both parents. In many people the development of T1D seems to take many years. Early onset suggests a major role for genetic factors, with a strong inverse association between age at diagnosis and prevalence of HLA alleles conferring susceptibility.<sup>112,113</sup> High genetic susceptibility in the proband implies increased genetic susceptibility and disease risk in his or her parents and siblings. This has been confirmed by many family studies.<sup>114</sup> Because genetic risk is inversely correlated with age at onset, it might be anticipated that this would also apply to familial risk. Most whites with T1D have genes called *HLA-DR3* (Human Leukocyte Antigen – DR isotype, III) or *HLA-DR4* (Human Leukocyte Antigen – DR isotype, IV). If you and your child are white and share these genes, your child's risk is higher. (Suspect genes in other ethnic groups

are less well studied. The *HLA-DR7* gene may put African Americans at risk, and the *HLA-DR9* gene may put Japanese at risk.) Individuals at high risk can be identified using immunologic, genetic, and metabolic parameters. In addition, circulating antibodies to pancreatic β-cell antigens are markers of islet autoimmunity. In first-degree relatives of persons with T1D, the levels and range of antigen specificities of these islet antibodies reflect the risk for clinical diabetes.<sup>115</sup> Besides, severe metabolic decompensation, rapid failure of C-peptide secretion, and high levels of glutamic acid decarboxylase are useful parameters.<sup>112</sup>

T2D accounts for some 90% of all cases of diabetes.<sup>116</sup> It has a stronger link to family history and lineage than T1D, although it also depends on multiple environmental factors.<sup>117–120</sup> T2D tends to run in families, based on sociologic and genetic factors. In general, the lifetime risk of developing the disease is about 40% in the offspring of one parent with T2D, greater if the mother is affected,<sup>121</sup> and approaching 70% if both parents have diabetes. It also shows that first-degree family history is associated with a twofold increased risk of future T2D.<sup>122,123</sup> People with certain rare types of T2D have different risks. If patients have the rare form called maturity-onset diabetes of the young (MODY), their child has a 50% chance of getting it too. The concordance of T2D in monozygotic twins is about 70%, compared with 20% to 30% in dizygotic twins.<sup>124,125</sup>

It should be noted that various single genetic variants have been found to be associated with increased risk for T2D, as mentioned earlier; however, the magnitude of increased risk conferred by each variant is relatively small. Thus, genetic testing for the prediction of T2D in high-risk individuals is currently of little value in clinical practice.

## Familial Obesity

Obesity also tends to run in families; hence family history is a basic tool in assessment.

BMI is the most common way to estimate body fat based on comparing a person's weight to height. Body fat can be measured in other ways in addition to BMI, including waist circumference, calculation of waist-to-hip circumference ratios, measuring the thickness of a skinfold (a pinch of skin and fat), and techniques such as ultrasound, which are more precise than BMI. Obesity is defined differently for children and teens than for adults. Children are still growing, and boys and girls mature at different rates. BMI for children and teens compares their heights and weights against growth charts that take age and sex into account. This is called a BMI-for-age percentile. A child's or teen's BMI-for-age percentile shows how his or her BMI compares with that of other boys and girls of the same age. For more details, see <http://www.nhlbi.nih.gov/health/health-topics/topics/obe/diagnosis>. Heritability estimates for obesity are high (typically >0.70). In addition, the use of quantitative obesity subphenotypes that can be accurately measured has resulted in significant measures of heritability for skinfold thickness,<sup>126–128</sup> waist circumference,<sup>129</sup> and total and regional fat distribution.<sup>130</sup>

The location of fat deposition, variation in the secretion of adipokines, and other factors govern whether a particular obese person is more predisposed to obesity-associated diseases and thus is “at risk.” Physiologically, metabolically deleterious and life-threatening forms of obesity are associated with a preferential accumulation of fat in the visceral adipose tissue and with ectopic fat deposition in insulin-sensitive tissues such as muscle, liver, and pancreas. This aberrant fat content strongly correlates with severe generalized insulin resistance and the development of a chronic inflammatory state, partly due to the infiltration of the adipose tissue by macrophages.<sup>131</sup> An anti-inflammatory adiponectin is known to strongly modulate the risk of the metabolic syndrome and T2D associated with obesity (diabesity).<sup>132</sup> Variation within the adiponectin gene is reported to modulate plasma adiponectin levels and also to predict risk for diabesity and associated CAD.<sup>133</sup> Paradoxically, the adiponectin variant alleles that protect against the development of diabesity by maintaining high adiponectin concentrations are also associated with obesity risk in both adults and children.<sup>134</sup> Individuals with high adiponectin levels can be severely obese but seem to enjoy metabolic protection.<sup>135</sup> The same alleles – together with the T2D protective PPAR $\gamma$ -12Ala allele – associate with a CAD-protective risk factor pattern, elevated adiponectin and insulin sensitivity, but also with a dramatic increase of 3 units of BMI.<sup>136</sup>

Several biomarkers have been used for assessing the development of obesity and its sequelae. These markers include ACE, AGEs, aldo-keto reductase family 1, member B10 (AKR1B10), alpha-methylacyl-CoA racemase (AMACR), cocaine- and amphetamine-regulated transcript (CART), collagen type I alpha 1, cannabinoid receptor 1 (CR1), ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1), MC4R, MTHFR (5,10-methylenetetrahydrofolate reductase [NADPH]), NRs (nuclear receptors), POMC, PPAR $\gamma$  (peroxisome proliferative activated receptor  $\gamma$ ), TCF7L2 (transcription factor 7-like 2 [T-cell specific]), TGF $\beta$ 1 (transforming growth factor  $\beta$ 1), VDR (vitamin D3 receptor).<sup>137</sup> However, the value of these biomarkers in risk assessment remains limited.

## RISK MANAGEMENT

### Familial Hypercholesterolemia

If they are diagnosed and treated early in childhood, individuals with FH can have a normal life expectancy. Early treatment of FH can reduce LDL burden, improve endothelial function, substantially attenuate the progression of atherosclerosis, and offer health and socioeconomic benefits.<sup>138–143</sup> Furthermore, long-term follow-up from statin trials, albeit not specifically in FH patients, suggests a legacy effect – that is, better CAD outcomes in those initially randomized to statin treatment.<sup>144,145</sup>

Children with HeFH should be treated with a fat-modified, heart-healthy diet at diagnosis and begin statins at age 8 to 10 years. For children aged 8–10 years, it is recommended to reduce LDL by 50% from pretreatment levels. For children above age 10, especially if there are additional cardiovascular risk factors including elevated lipoprotein(a), the target LDL

should be less than 3.5 mmol/L (130 mg/dL). In HoFH, pharmacologic treatment should start at diagnosis. Children with HoFH should be referred to and cared for at a specialized center.<sup>146</sup>

Diet and lifestyle underpin the management of FH in children. In considering dietary fat content, the major dietary drivers of serum cholesterol levels are saturated fats and trans fats with a small contribution from dietary cholesterol.<sup>147,148</sup> Limitation of foods high in saturated fat will secondarily limit dietary cholesterol intake; cholesterol-containing foods without saturated or trans fats may be allowed (<http://www.health.gov/dietaryguidelines/2015-scientific-report/>). There should be annual or biannual monitoring of weight, growth, and developmental milestones. Physical activity should be promoted and smoking strongly discouraged. Identifying children with FH early ensures that adherence with lifestyle interventions is established before puberty. Other cardiovascular risk factors should be monitored and treated if indicated.

The most powerful cholesterol-lowering agents for FH are the statins. By inhibiting *de novo* cholesterol synthesis at HMG-CoA reductase, compensatory upregulation of LDLR lowers plasma LDL concentration. Statins are the cornerstone of FH management. Simvastatin, lovastatin, atorvastatin, pravastatin, fluvastatin, and rosuvastatin are approved in the United States and Europe for use in children with FH. Treatment should be initiated at the lowest recommended dose and titrated upward according to the LDL-lowering response and tolerability. Ezetimibe, a recently developed drug that limits cholesterol absorption, lowers LDL by about 15%. In addition, bile acid sequestrants that waste more bile acids for the patient result in a reduction of the cholesterol pool in cells. Thus the addition of ezetimibe or a bile-acid sequestrant may be required to attain the LDL goal in some patients.<sup>149–151</sup>

Modern pharmacotherapy can achieve desirable concentrations of LDL in HeFH, but treatment for HoFH remains problematic. Patients with HeFH respond as do normal subjects to lipid-modifying treatment as there is a functional LDLR that will clear LDL from plasma. In 2013, both mipomersen, an ApoB antisense oligonucleotide, and lomitapide, a microsomal triglyceride protein inhibitor, were approved for the treatment of HoFH in the United States.<sup>152</sup> Lomitapide was also approved in Europe. Also, PCSK9 inhibitors, including evolocumab and alirocumab, were approved in Europe and United States in 2015. More recently, a small, open label study of evinacumab, a fully human ANGPTL3-blocking antibody, demonstrated a mean reduction of LDL by 49%.<sup>153</sup> Besides, liver transplantation (alone or in combination with a heart transplant) may be considered for young HoFH patients, although the disadvantages of this approach include the high risk of post-transplantation complications and mortality as well as the limited availability of donors. Other options, such as partial ileal bypass and portacaval shunting, are not recommended for this population but may be considered for patients with very severe disease in whom other conventional options are not effective.<sup>146,154</sup> In addition, several other novel options for the treatment of HoFH, such as gene therapy, and gene editing are being investigated. Gene therapy is a strategy used

to correct defective genes responsible for the development of disease, while gene editing utilizes the CRISPR/Cas9 system to edit a mutated gene copy. For example, replacement of the *LDLR* gene has the potential to decrease LDL levels while also making patients with HoFH more responsive to conventional therapies.<sup>155</sup> Preclinical studies using mouse models of HoFH and HeFH have yielded promising results.<sup>156</sup> Other preclinical studies have utilized the CRISPR/Cas9 system delivered by adeno-associated virus (AAV) to edit the *Ldlr* gene and demonstrated amelioration of the atherosclerosis phenotype in *Ldlr* mutant mice.<sup>157</sup> Currently there is a Phase I trial of a novel AAV vector with human low-density lipoprotein receptor (*hLdlr*) gene that at the writing of this chapter is ongoing (<https://clinicaltrials.gov/ct2/show/NCT02651675>).

## Familial Hypertension

Treatment of familial hypertension should comprise both lifestyle modification and pharmacologic therapy. The primary goal of hypertensive treatment is to reduce the stress placed on arterial walls, which in turn can reduce the continued inflammation within arterial walls, resulting in reduced levels of plaque build-up. Clinical trials have demonstrated that hypertensive control results in decreased rates of stroke, myocardial infarction, and heart failure.<sup>158</sup>

Pharmacologic therapy follows the guidelines for the treatment of essential hypertension. The best strategy is to formulate a combination therapy that targets different physiologic mechanisms and accounts for patient comorbidities. Based on either the approved responses of the family members to a given drug or genetic testing in the patient's family, the medication targeting the factor related to the primary genetic alteration should be tested first rather than following the general guideline for hypertension treatment, in which the preferred initial drug choices are ACE inhibitor in patients less than 55 years old, or a dihydropyridine calcium channel blocker (CCB) in patients older than 55 or African-American patients of any age. These options can then be trialed in combination and titrated as necessary before adding a thiazide, including a recently approved thiazide-like diuretic such as chlorthalidone and indapamide as the third medication. Spironolactone is recommended as the fourth antihypertensive drug.<sup>159,160</sup> Vasodilating β-blockers – that is, carvedilol and labetalol – are the fifth-line drug therapy.<sup>161</sup> Other options include α-blockers, clonidine, methyldopa, and direct vasodilators such as hydralazine or minoxidil. These seldom form part of the routine management and should be prescribed only with expert advice. Adequate monotherapy controls hypertension in 30% of cases.<sup>161</sup> If monotherapy is insufficient, the regimen could be modified by altering dose or adding an additional class of drug. Triple therapy must be optimized before selecting further add-on therapy because optimal dosing and drug selection can see blood pressure normalize in many patients. Patients must be approached in a stepwise manner, beginning with traditional antihypertensive therapy followed gradually by additional agents to reach a quadruple or five-drug compound regimen if necessary. In those who remain hypertensive

despite thorough medical management, there are interventional options currently under development, such as renal denervation and carotid sinus stimulation, which are promising but require further research. The primary aim of antihypertensive treatment is to reduce the blood pressure to less than the 95th percentile and to less than the 90th percentile in the presence of comorbid conditions like diabetes, heart disease, or kidney disease.

## Familial Diabetes

Risk management of familial diabetes requires continuous medical care with multifactorial risk reduction strategies beyond glycemic control. The management plan should be formulated as a collaborative therapeutic alliance among the patient and family, the physician, and other members of the healthcare team. The management plan should recognize the role of education in diabetes self-management and ongoing diabetes support as integral components of care.<sup>162</sup>

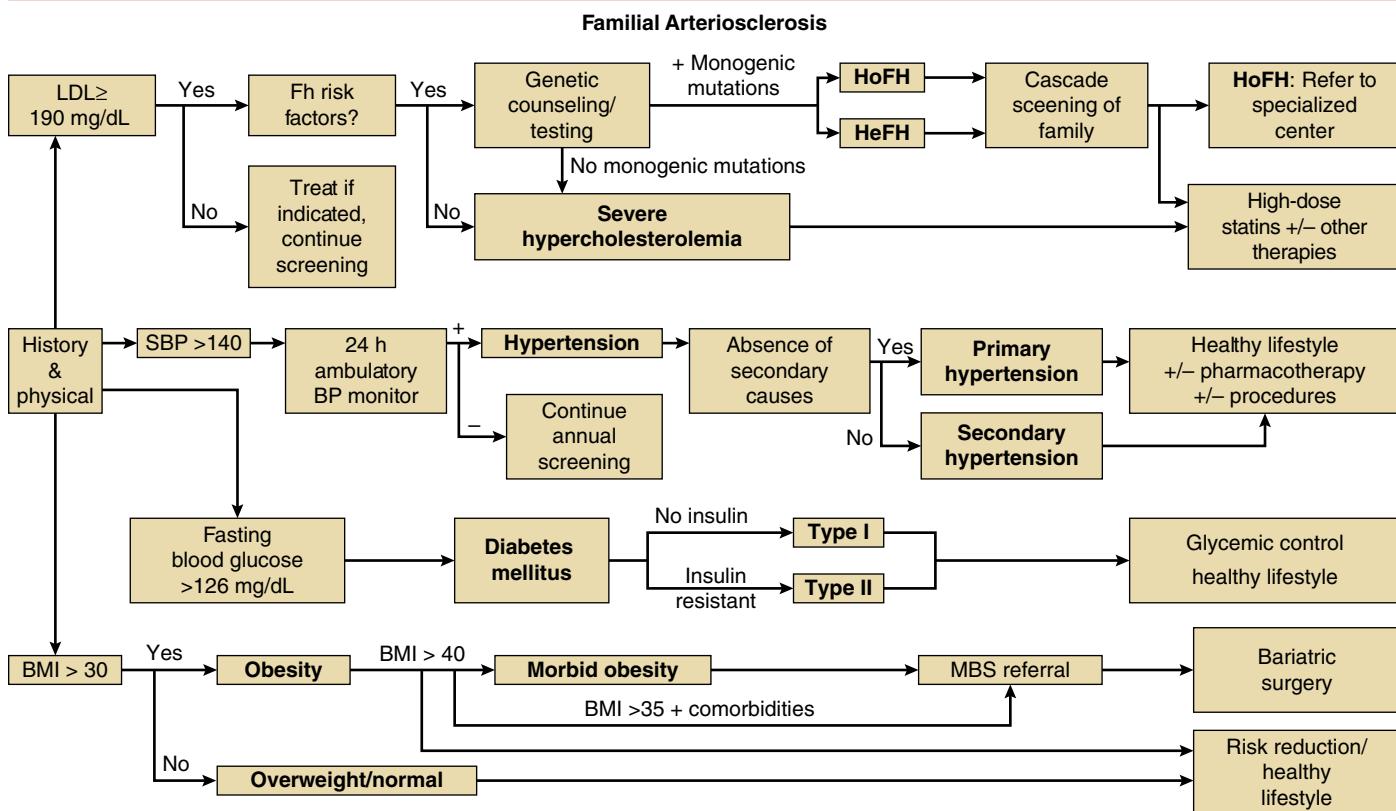
## Familial Obesity

The treatment of familial obesity should also focus on changing health behaviors to achieve effective weight management. Studies demonstrate modest weight loss of 5% to 10% with improvement in cardiometabolic parameters. Lifestyle interventions incorporating dietary change, increased physical activity, and decreased sedentary behaviors, with the involvement of family and adoption of a developmentally appropriate approach, should be used as the first line of treatment.

Drug treatment for obesity is an evolving branch of pharmacology. Several anti-obesity drugs are under testing. Sibutramine (a centrally acting serotonin/noradrenaline reuptake inhibitor that mainly increases satiety), orlistat (a pancreatic lipase inhibitor that reduces fat absorption by partially blocking the hydrolysis of dietary triglycerides), and rimonabant (a selective antagonist of cannabinoid type 1 receptor) are three examples. When properly used, these medicines contribute to the reduction of body weight and undoubtedly improve cardiometabolic risk factors. Patients who might benefit from anti-obesity treatment are those with a BMI ≥30 or 27 to 29.9 kg/m<sup>2</sup>.<sup>163</sup> It should be pointed out that the pharmacologic approach is a complement to the behavioral strategy aimed at changing a person's lifestyle. But to treat extreme obesity – that is, in persons with an overweight of more than 100 lb (BMI >40) – only bariatric surgery can be effective.

This chapter describes one of the major precursor diseases to cardiovascular disease: atherosclerosis. The pathogenesis of atherosclerosis involves the complex interplay between genetics, associated diseases, and social/environmental factors that all contribute to its development. It is imperative for clinicians to understand familial patterns of hyperlipidemia, hypertension, diabetes, and obesity to ensure early management of these precursor diseases in an attempt to lower the development of atherosclerosis and thus overall cardiovascular risk.

## CHAPTER ALGORITHM



Algorithm for the Diagnosis and Management of Familial Arteriosclerosis. *Fh*, familial hypercholesterolemia; *HoFH*, homozygous FH; *HeFH*, heterozygous FH; *SBP*, systolic blood pressure; *BP*, blood pressure; *BMI*, Body Mass Index; *MBS*, metabolic bariatric surgeon.

## SELECTED KEY REFERENCES

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# Smoking

SAMIR K. SHAH

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Called “one of the greatest public health catastrophes” of the 20th century in the Surgeon General’s semicentennial report, smoking has had profound health consequences that continue to be felt even as its North American prevalence decreases.<sup>1</sup> For vascular surgeons in particular, the association with aneurysm formation and arterial occlusive disease means that smoking remains one of the most critical modifiable risk factors.

## EPIDEMIOLOGY

Smoking is the foremost cause of preventable morbidity and mortality in the United States. Annually, more than 480,000 premature deaths and more than \$300 billion in lost productivity and direct costs are attributed to smoking.<sup>2</sup>

Although the prevalence of smoking in the United States has decreased by more than half since the Surgeon General’s seminal report on smoking in 1964, it remains significant.<sup>1</sup> Based on the National Health Interview Survey of almost 27,000 Americans at least 18 years of age, 14.0% smoked regularly in 2017, the lowest ever since measurement began in 1965. The prevalence was higher in males than females (15.8% vs. 12.2%). Adults aged 45 to 64 years had the highest rate of 16.5% compared with the lowest rate of 8.2% in those who were 65 years or older. There were also differences based on racial groups, education, and economic status. Namely, cigarette use was highest among American Indian/Alaska natives (24.0%) and lowest among Asians (7.1%). Non-Hispanic Whites had an intermediate rate of 15.2%. Americans with graduate degrees had a mere 4.1% use compared with 36.8% in those with a general equivalency diploma. Finally, people with an annual household income of less than \$35,000 had

a use rate of 21.4% versus 7.6% in those with corresponding incomes greater than \$100,000 living above the poverty line.<sup>3</sup>

It is important to recognize that patients may use tobacco products besides cigarettes. The 2017 National Health Survey demonstrated that the following products were used daily or some days: cigars, cigarillos, filtered little cigars (3.8%); electronic cigarettes (2.8%); snuff, dip, and other smokeless tobacco (2.1%); pipes, water pipes and hookahs (1%).<sup>3</sup>

A recent increasingly popular cigarette alternative is the electronic cigarette or e-cigarette. E-cigarettes, while tobacco-free, are battery-operated devices that deliver aerosolized nicotine (“vaping”). They are marketed both as cigarette alternatives and as smoking cessation tools. Although more than half of smokers who attempted to quit had used e-cigarettes in 2014,<sup>4</sup> no such device has been FDA-approved for smoking cessation, and the United States Preventative Services Task Force has found inadequate evidence to support e-cigarettes as cessation tools.<sup>5</sup> As a corollary, data regarding potential long-term harms from inhaling nicotine vapors are also absent. Finally, there is concern that e-cigarette use in minors may translate into long-term nicotine addiction for future generations.

## BIOLOGIC EFFECTS OF SMOKING ON THE VASCULATURE

Cigarette smoke has adverse effects on vascular biology through a variety of mechanisms. First, it creates endothelial dysfunction, including reduction of the availability of nitric oxide, and activation of enzymes leading to the increased production of reactive oxygen species. Flow-mediated dilation, a common

measure of endothelial function, is diminished in active smokers and even nonsmokers exposed to secondhand smoke for less than 1 hour.<sup>6</sup>

Second, smoking creates a prothrombotic environment. Smoking leads to the increased production of thromboxane A<sub>2</sub> and decreased levels of prostacyclin, thus overall promoting platelet aggregation. Smoking is also associated with elevated levels of prothrombotic substances such as von Willebrand factor, thrombin, and fibrin, while simultaneously reducing antithrombotic and fibrinolytic substances such as tissue plasminogen activator and plasminogen activator inhibitor-1. Smokers also have higher markers of platelet activation, which decline after smoking cessation.<sup>7,8</sup>

Last, smoking promotes an inflammatory state, which has been associated with vascular disease. Compared with non-smokers, smokers have higher levels of leukocytes, C-reactive protein, interleukin-6, tissue necrosis factor- $\alpha$ , interleukin-1- $\beta$ , and other inflammatory markers.<sup>9,10</sup>

It should also be noted that nicotine itself plays an important role in known drivers of vascular disease. Not only does it act as a sympathomimetic substance that raises blood pressure, but it is also associated with insulin resistance, altered lipid metabolism, and endothelial dysfunction.<sup>1</sup> Finally, vascular surgeons have for generations passed on the observation of differential disease distribution patterns between patients who smoke versus those with diabetes. Smokers tend to have aortoiliac and superficial femoral disease, while occlusive atherosclerosis generally strikes the profunda and tibials in diabetic patients.<sup>11</sup> However, rigorous documentation of these broad and frequently variable differential disease patterns is sparse.

## NONVASCULAR CLINICAL EFFECTS

Smoking has causal links with numerous diseases across several organ systems. Most prominently, smoking is associated with cancers of the lungs, oropharynx and larynx, esophagus, stomach, pancreas, kidney, bladder, and cervix. More recently, it has been implicated in liver and colorectal cancers as well.<sup>1</sup>

Cigarette smoking also has been linked to diabetes, cataracts, macular degeneration, chronic obstructive pulmonary disease, asthma, and rheumatoid arthritis, among others.

## VASCULAR CLINICAL EFFECTS

### Development of Peripheral Arterial Disease

Cigarette smoking has an unequivocal positive association with the development of peripheral vascular disease in multiple large epidemiologic studies. For example, the original Framingham Study, which followed 5209 subjects, showed that smoking was more strongly associated with the development of intermittent claudication than even coronary artery disease and stroke.<sup>12</sup> Similarly, the Speedwell study followed 2348 men starting in 1979 and found that smoking was the strongest risk factor for the development of claudication, more so than diabetes and hypertension.<sup>13</sup>

The Women's Health Study provided additional insights into the development of peripheral arterial disease (PAD). This study prospectively followed nearly 40,000 healthy female health professionals at least 45 years of age beginning in 1993.<sup>14</sup> During a median follow-up of 12.7 years, 178 subjects developed symptomatic PAD. Multivariate analysis showed that the risk was dose-dependent with respect to smoking. Compared with never smokers, the hazard ratio for symptomatic PAD development was 3.16 for former smokers, 11.94 for current smokers using fewer than 15 cigarettes, and 21.08 for those using 15 or more cigarettes daily.

Interestingly, the Women's Health Study also showed that smoking cessation was beneficial with respect to PAD development, and that these benefits were proportional to the duration of cessation. Using current smokers as the reference group, the hazard ratios for PAD development in those who had fewer than 10 years of cessation, 10 to 19 years of cessation, 20 or more years, and never smokers were 0.39, 0.28, 0.16, and 0.08, respectively.<sup>14</sup> Not all studies, however, have found that cessation reduces atherosclerotic disease burden risk. The Atherosclerosis Risk in Communities study showed that after controlling for pack-years of smoking, there was no difference in atherosclerotic disease between past and current smokers as measured by carotid artery intimal-medial thickness.<sup>15</sup>

### Graft Failure and Amputation

Willigendael et al. conducted a meta-analysis to determine the effects of smoking on the patency of lower extremity arterial grafts.<sup>16</sup> On the basis of a total of 20 prospective and retrospective studies, the hazard ratio for graft failure was 2.35 in smokers compared with nonsmokers. Studies that used biochemical tests to determine smoking status found an even higher hazard ratio of 3.8, implying that studies based on self-reported smoking status may underestimate effects. Interestingly, three component studies that looked at the effect of patient age all found that smoking in patients less than 65 years old had a higher risk of graft failure than older patients. Smoking had similarly negative effects on autogenous grafts and polyester grafts.

Willigendael's meta-analysis also found that there was a graft patency benefit to smoking cessation. Former smokers had patencies superior to those of current smokers and comparable to never smokers.<sup>16</sup>

In a corollary study, Lassila et al. prospectively examined the impact of heavy smoking, defined as 15 or more cigarettes daily, on amputation risk and survival in 190 patients undergoing lower extremity arterial reconstruction for PAD. At 3 years, heavy smokers had diminished survival and increased major amputation rates (21% vs. 2% in non-heavy smokers,  $P < 0.001$ ).<sup>17</sup>

### Smoking and Other Vascular Disease

Although this chapter focuses on atherosclerotic occlusive peripheral vascular disease, it should be noted that smoking is also intimately associated with two other diseases of concern to the vascular surgeon: thromboangiitis obliterans (Buerger

disease) and aortic aneurysms. Both of these are common and important pathologies worldwide and are described in more detail in separate chapters.

## SMOKING CESSATION

Smoking cessation can have positive health effects, including an improvement in all-cause mortality.<sup>18</sup> Although duration of cessation counseling from a healthcare provider correlates with likelihood of abstinence, providers would be mistaken to believe that extensive time investments are necessary to have an impact: even individualized interventions as short as 1 minute have been shown to increase quitting success.

Although a full treatment of cessation interventions is beyond the scope of this work, some essential guidelines follow. The Agency for Healthcare Research and Quality recommends that smoking interventions should consist of five key elements, the five “A’s: ask, advise, assess, assist, and arrange.<sup>18</sup> Physicians should ask about and document tobacco use at every patient visit. They should directly advise every tobacco user to quit. Each tobacco user should be assessed for his or her willingness to quit. Patients willing to quit should receive assistance, detailed below, and finally healthcare providers should arrange for follow-up.

For patients who are unwilling to quit, physicians should be sure to use motivational interview strategies along with the five “R’s.<sup>18</sup> Physicians should point out the relevance of quitting to the patient with regard to his or her social situation, health concerns, and so forth. They should delineate the risks of ongoing tobacco use and point out the manifold rewards of quitting. Finally, the physician should ask the patient to identify roadblocks to success and attendant solutions, and repeat this intervention at each visit.

For patients interested in quitting, physicians should provide contemporary practical advice (Table 11.1), and select medication adjuncts. There are currently seven FDA-approved first-line therapies consisting of five nicotine-replacement medications – gum, inhaler, lozenge, nasal spray, and transdermal patch – and two non-nicotine pharmaceuticals, bupropion SR, and varenicline (Table 11.2).<sup>18</sup> Bupropion SR blocks neuronal reuptake of dopamine and norepinephrine while also serving as a nicotinic acetylcholinergic receptor antagonist. Varenicline functions as a partial mixed nicotine receptor agonist and antagonist. Unfortunately, there is no consensus on how to choose among first-line therapies, and the final decision may ultimately reflect personal preference and practical matters such as insurance coverage.

It should be noted that evidence does not support the use of any of these therapies in smokers who use fewer than 10 cigarettes daily. Also, several combinations of first-line therapies have been demonstrated to be effective: nicotine patch for more than 14 weeks and nicotine gum or spray, nicotine patch and nasal inhaler, and nicotine patch and bupropion

**TABLE 11.1** Practical Advice in Smoking Cessation

- Aim for total abstinence after the chosen quit date.
- Alcohol decreases success rates; consider reducing alcohol intake.
- Others in the patient’s household should consider attempting to quit or not smoking in the presence of the patient to maximize success.
- Identify triggers for smoking and avoid them.
- Anticipate withdrawal symptoms – problems with mood and concentration, nausea, headache – which will peak at 1–2 weeks but may persist for longer periods.

**TABLE 11.2** Nicotine and Non-nicotine Therapy for Smoking Cessation<sup>20–24</sup>

Medication	Directions	Dosing	Major Side Effects
<b>Nicotine Replacement Therapy for Smoking Cessation</b>			
Nicotine gum	Chew gum until it tingles, then park between cheek and gums until tingle disappears, then chew again until tingle returns. Repeat until most of tingle is gone (~30 min).	Use 2-mg pieces for <25 cigarettes daily or 4-mg pieces for >25 cigarettes daily. Smokers should use at least one piece every 1–2 h for the first 6 weeks; the gum should be used for up to 12 weeks with no more than 24 pieces to be used per day.	Throat and mouth irritation, increased salivation, hiccuping, jaw muscle ache Use with caution in patients with oral or pharyngeal inflammation and in patients with a history of esophagitis or peptic ulcer.
Nicotine lozenge	Use 2-mg lozenges for first cigarette use >30 min after waking or 4-mg pieces for <30 min after waking. Allow lozenge to dissolve (~20–30 min) in mouth. Do not chew or swallow lozenge. Occasionally move lozenge from one side of mouth to the other.	Weeks 1–6: 1 lozenge every 1–2 h; at least 9 but no more than 20 lozenges/day. Weeks 7–9: 1 lozenge every 2–4 h Weeks 10–12: 1 lozenge every 4–8 h	Throat and mouth irritation, increased salivation, hiccuping, indigestion. Use with caution in patients with oral or pharyngeal inflammation and in patients with a history of esophagitis or peptic ulcer.
Nicotine inhaler	10-mg cartridges (4 mg is delivered) to be used for inhalation. Inhale deeply into back of throat or puff in short breaths. Nicotine in cartridge is used up after 20 min of active puffing.	Initial 12 weeks, 6–16 cartridges per day, then gradual reduction during 6–12 weeks	Throat and mouth irritation, coughing, rhinitis, sinusitis, pain in jaw and neck. Use with caution in patients with bronchospastic disease.

*Continued*

**TABLE 11.2** Nicotine and Non-nicotine Therapy for Smoking Cessation<sup>20–24</sup>—cont'd

Medication	Directions	Dosing	Major Side Effects
Nicotine nasal spray	50-μL spray containing 0.5 mg of nicotine per actuation. One dose is 1 mg of nicotine (2 sprays, one in each nostril). Spray once in each nostril, do not sniff or inhale while spraying.	Initially 1–2 doses per hour up to 5 doses per hour (40 doses per day) for 8 weeks, with tapering during next 4–6 weeks.	Use with caution in patients with bronchospastic disease, known chronic nasal disorders (allergy, rhinitis, nasal polyps, sinusitis).
Transdermal nicotine patch	Wear patch 16 or 24 hours, 24 h if cravings on awakening, otherwise remove at bedtime and apply fresh patch on a clean, nonhairy area of skin between neck and waist in the morning. Do not reapply patch to a previously used skin site for at least 1 week. Do not cut patch into smaller pieces.	10-week therapy for >10 cigarettes a day, 8-week therapy for <10 cigarettes a day 10-week therapy: 21 mg for 6 weeks, 14 mg for 2 weeks, 7 mg for 2 weeks 8-week therapy: 14 mg for 6 weeks, 7 mg for 2 weeks	Skin irritation
Medication	Mechanism of Action	Dosing	Major Side Effects
<b>Non-nicotine Therapy for Smoking Cessation<sup>17,19</sup></b>			
Bupropion (Zyban)	Atypical antidepressant with dopaminergic and adrenergic actions	Start with 150 mg daily for first 3 days and increase to 150 mg twice daily. The maximum dose of bupropion is 300 mg per day. Treatment should be started while the patient is still smoking; the patient should set a target quit date, usually for the second week of treatment.  Continue treatment for 7–12 weeks. Patients abstinent within 7–12 weeks may continue with 300 mg daily maintenance therapy.  May be used in combination with nicotine replacement therapy.	Seizures, worsening depression, anxiety, agitation, irritability, insomnia, unusual changes in behavior, development of suicidal ideation/behavior, hypertension, dry mouth.  Contraindicated in patients with seizure disorder already taking bupropion for another reason as risk of seizures are dose dependent with bulimia or anorexia, undergoing abrupt discontinuation of alcohol or sedatives, taking monoamine oxidase inhibitors, allergic to bupropion.  Use with extreme caution in patients with hepatic dysfunction. <b>Warning: Patients should be closely monitored for signs of serious neuropsychiatric side effects.</b>
Varenicline (Chantix)	α <sub>4</sub> β <sub>2</sub> Nicotinic acetylcholine receptor partial agonist	Treatment should be started while the patient is still smoking; the patient should set a target quit date, usually for the second week of treatment.  Days 1–3: 0.5 mg once daily 4–7: 0.5 mg twice daily 8–end: 1 mg twice daily  Adjust dosage for severe renal impairment or side effects to maximum dose of 0.5 mg twice daily.  Initial therapy for 12 weeks with an optional additional 12 weeks for maintenance therapy.	Nausea, insomnia, unusual or vivid dreams, constipation, headaches, weight gain, gas, changes in behavior, agitation, depressed mood, suicidal ideation.  <b>Warning: Patients should be closely monitored for signs of serious neuropsychiatric side effects.</b>

From: <https://www.gskhealthpartner.com/en-us/respiratory-health/brands/nicotine-replacement-therapy/nicorette-lozenges/nicorette-lozenges-dosing-administration/>

SR.<sup>18</sup> Effectiveness of individual therapies and combinations are listed in Table 11.3.

Since the first evidence linking smoking and lung cancer more than 60 years ago, there have been extraordinary efforts to elucidate the clinical effects, mechanisms of disease, and public

health impact of smoking. Concerted efforts to curb smoking rates based on broad scientific consensus on the adverse effects of smoking have produced steady declines in smoking rates. Nevertheless, there remains much to be done. As surgeons, we are uniquely positioned and obligated to counsel patients

**TABLE 11.3** Outcomes of Selected Smoking Cessation Interventions<sup>18</sup>

Medication	Estimated Odds Ratio of Abstinence Success at 6 months Post-quit (95% CI)	Estimated Abstinence Rate at 6 months Post-quit (95% CI)
Placebo	1.0	13.8
Nicotine Patch (>14 weeks) + Nicotine Gum or Spray	3.6 (2.5–5.2)	36.5 (28.6–45.3)
Varenicline (2 mg/day)	3.1 (2.5–3.8)	33.2 (28.9–37.8)
Nicotine Patch + Bupropion SR	2.5 (1.9–3.4)	28.9 (23.5–35.1)
Nicotine Nasal Spray	2.3 (1.7–3.0)	26.7 (21.5–32.7)
Nicotine Patch + Nicotine Inhaler	2.2 (1.3–3.6)	25.8 (17.4–36.5)
Nicotine Inhaler	2.1 (1.5–2.9)	24.8 (19.1–31.6)
Bupropion SR	2.0 (1.8–2.2)	24.2 (22.2–26.4)
Long-Term Nicotine Patch (>14 weeks)	1.9 (1.7–2.3)	23.7 (21.0–26.6)
Nicotine Patch (6–14 weeks)	1.9 (1.7–2.2)	23.4 (21.3–25.8)
Nicotine Gum	1.5 (1.2–1.7)	19.0 (16.5–21.9)

not only during “teachable moments” in their lives, as before surgery, but also longitudinally.<sup>19</sup> Indeed, smoking cessation must be seen by surgeons to be as crucial to improving patients’ health as any surgical intervention.

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# Less Commonly Considered Causes of Atherosclerosis

AMIR F. AZARBAL and GREGORY L. MONETA

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Atherosclerotic disease is the leading cause of mortality in developed countries. Better understanding of the pathophysiology of atherosclerosis has led to successful therapies and preventative strategies; however, treatment of conventional risk factors for atherosclerotic disease may only prevent 50% of cardiovascular events.<sup>1</sup> A more complete understanding of atherosclerotic risk factors and the atherosclerotic process has the potential to yield improved therapies and preventative strategies.

Several less commonly considered areas of investigation have added insights into the development and progression of atherosclerosis. First, the atherosclerotic lesion itself appears to be more complex than previously described, and the roles of macrophages, vascular smooth muscle cells (VSMCs) and endothelial cells are not as distinct and static as once thought. Second, the effect of hyperlipidemia on atherosclerosis formation appears to involve more than just low- and high-density lipoprotein (HDL) levels. Finally, less commonly considered environmental exposures as well as the interaction between diet and the gut microbiome seem to be associated with atherosclerosis and conventional atherosclerotic risk factors such as diabetes mellitus (DM; Table 16.1).

## **THE ATHEROSCLEROTIC LESION**

The prevailing model for the progression of the atherosclerotic lesion from fatty streak to mature plaque has been well described.<sup>2,3</sup> In short, injury to the vascular endothelium allows for adherence and transmigration of bone marrow-derived monocytes into the arterial wall. Monocytes within the arterial wall differentiate into macrophages that phagocytose oxidized LDL (ox-LDL), and become lipid-rich foam cells. VSMCs within the arterial media migrate toward the luminal surface of the plaque to form a fibrous cap. The degree of inflammation, lipid content, and fibrous cap thickness within the lesion affect the stability of the plaque.

Recent evidence suggests that the roles of endothelial cells, VSMCs, and macrophages may not be as static as suggested by this model. Under atherogenic conditions, endothelial cells can transition into fibroblast-like cells, while VSMCs can transition to an inflammatory phenotype resembling macrophages.<sup>4,5</sup> It is difficult to determine the degree to which foam cells are derived from macrophages versus VSMCs *in vivo*, as the two cells are difficult to distinguish based on traditional cell surface markers. VSMC-derived foam cells express cell surface markers typically

**TABLE 16.1****Less Commonly Considered Causes of Atherosclerosis****Residual Hyperlipidemia**

Lipoprotein a

**Diet**

Trimethylamine oxide (TMAO)

**Human Gut Microbiome****Infection****Bacteria***Chlamydia pneumoniae, Helicobacter pylori*

Periodontitis-causing bacteria

**Viruses**

HSV, CMV, EBV, HCV, enteroviruses

**Environmental****Persistent organic pollutants**

Dioxins

Polychlorinated biphenyls (PCBs)

**Air pollution****Heavy metals**

Arsenic, cadmium, mercury

CMV, cytomegalovirus; EBV, Epstein–Barr virus; HSV, herpes simplex virus; HCV, hepatitis C virus.

seen on macrophages, such as CD68 and Mac-2 antigen, while downregulating typical VSMC markers, such as alpha-smooth muscle cell actin.<sup>6–9</sup> These altered VSMCs can phagocytose ox-LDL to become lipid-rich foam cells, and contribute to the progression of atherosclerotic lesions through increased cellular apoptosis, and dysfunctional reverse cholesterol transport.<sup>10–12</sup> Therefore it seems that VSMCs can undergo both compensatory and pathologic changes during the atherosclerotic process, by both forming the fibrous cap of the atherosclerotic lesion and contributing overall plaque stability while also contributing to the foam cell population of the atherosclerotic lesion.<sup>13</sup> The varying effects of VSMCs in atherosclerotic lesions may be partially explained by the fact that VSMCs are not a homogenous population derived only from the arterial media. Rather, VSMCs can be derived from precursor cells in the bone marrow, adventitia, or arterial media, with VSMCs of different origins producing different effects within the atherosclerotic lesion.<sup>14–16</sup> A better understanding of the role of various VSMC populations in the formation of atherosclerosis may potentially lead to new therapies that can enhance the protective effects of VSMCs while decreasing the harmful effects.

## HYPERLIPIDEMIA

Hyperlipidemia is one of the most well-known risk factors for atherosclerotic disease and a primary target of pharmacologic intervention for preventing or slowing the atherosclerotic process. High LDL cholesterol and low HDL cholesterol have been the most-studied lipid components related to atherosclerotic disease. Total cholesterol and LDL reduction has been the cornerstone of medical treatment and prevention of ischemic heart disease with an abundance of randomized control trials

that attest to efficacy of cholesterol lowering therapy in preventing ischemic heart disease.<sup>17–20</sup> However, additional lipid variables have emerged as risk factors for atherosclerotic heart disease and potential routes of residual risk reduction.

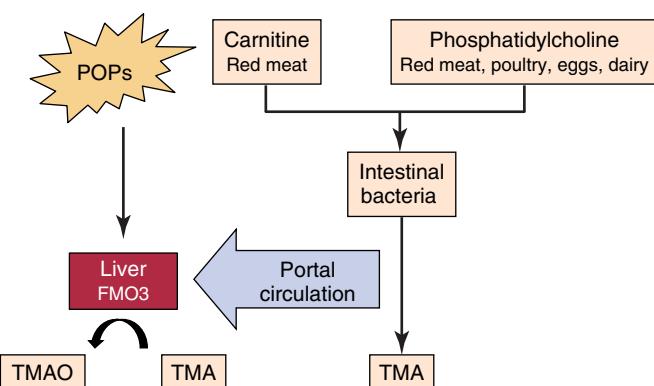
## Lipoprotein a

Lipoprotein a, or Lp(a), consists of an LDL-like molecule linked to apolipoprotein (a), or Apo(a). Oxidized phospholipids of the LDL-like moiety are proatherogenic and proinflammatory, while the Apo(a) moiety is a plasminogen-like glycoprotein with prothrombotic effects. There are several different isoforms of Apo(a) and therefore of Lp(a) as well. Lp(a) levels correlate with both primary and secondary cardiovascular events independent of LDL and HDL levels.<sup>21–24</sup> Statin medications and niacin can reduce Lp(a) levels modestly.<sup>25–28</sup> Further reductions in Lp(a) can be achieved through apheresis, which can be used to remove both LDL and Lp(a) particles or Lp(a) particles alone. Lp(a)-specific apheresis may be able to prevent progression of angiographically measured coronary atherosclerosis and decrease major adverse cardiovascular (MACE) events when added to maximal medical therapy.<sup>29–32</sup> The more recent development of subcutaneously-administered antisense oligonucleotides capable of reducing Lp(A) levels may provide a more practical and widely-applicable means of Lp(a) reduction compared to apheresis.<sup>33–35</sup> Given that conventional therapy with statins may reduce only half of cardiac adverse events,<sup>1</sup> there seems to be a potential role for the consideration of lipid parameters beyond HDL and LDL and additional lipid-based interventions.

## DIET

A diet low in meats and animal products is a component of a low-fat, low-cholesterol diet. However, there may be a link between diet and atherosclerosis beyond dietary cholesterol intake. Trimethylamine-N-oxide (TMAO) is a proatherogenic molecule that is derived from carnitine, which is predominantly found in red meats, and phosphatidylcholine (PC), which is found in most animal products including dairy and eggs. Intestinal bacteria synthesize trimethylamine (TMA) from carnitine and PC. TMA is transported to the liver via the portal circulation, where it is converted to the proatherogenic molecule TMAO by a family of enzymes known as the flavin mono-oxygenases (FMO), particularly FMO3. The FMOs also oxidize a wide range of drugs and environmental toxins, such as persistent organic pollutants (POPs) in pesticides, and there may be a synergistic effect of diet and environmental toxins on atherosclerosis formation (Fig. 16.1).

The production of TMAO from dietary precursors is dependent on intestinal bacterial metabolism and can be suppressed by antibiotic administration.<sup>35</sup> The amount of animal products in the diet affects the intestinal microbiome and the amount of TMAO produced. Vegetarians and vegans produce significantly less TMAO than omnivores, and even short-term changes in diet can alter intestinal microbial populations.<sup>36,37</sup> Therefore, there appears to be a positive feedback loop whereby the



**Figure 16.1** Interaction Between Diet and Environment. Carnitine and phosphatidylcholine are converted into trimethylamine (TMA) by intestinal bacteria. TMA is oxidized by the flavin mono-oxygenase 3 (FMO3) in the liver into trimethylamine-N-oxide (TMAO). FMO3 is also upregulated by persistent organic pollutants (POPs).

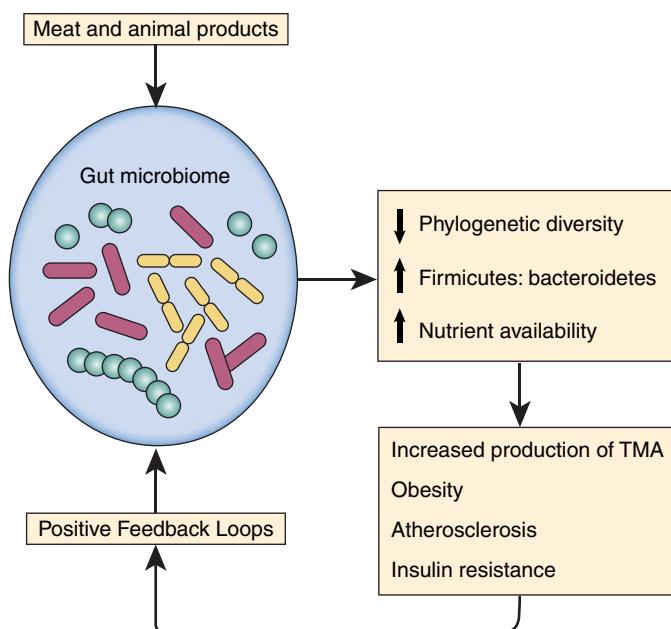
consumption of animal products leads to TMAO production and causes an increase in the bacterial populations responsible for TMAO production.

Dietary TMA and choline supplementation also induce atherosclerosis in animal models,<sup>38</sup> and blood TMAO levels are associated with increased rates of PAD, MI, MACE, CAD, and overall mortality in human studies.<sup>35,39–42</sup> Increased consumption of TMAO precursors, PC and L-carnitine, is also associated with increased atherosclerotic diseases and cardiovascular-specific mortality in animal models and several large human studies.<sup>43–45</sup>

On the whole, the observational and animal data are highly suggestive of a role for PC, carnitine, and TMAO in atherosclerosis formation. However, there is some seemingly contradictory evidence regarding the association between TMAO and atherosclerosis. L-carnitine supplementation, while increasing TMAO production may prevent atherosclerosis in animal models,<sup>46</sup> and L-carnitine supplementation in patients with acute MIs decreases all-cause mortality.<sup>47</sup> Some studies of meat consumption have also suggested that an increased risk of cardiovascular disease and diabetes is not associated with fresh or frozen meat consumption, but is limited to consumption of processed meats.<sup>48–50</sup> These studies did not account for the effect of non-meat animal products that lead to increased TMAO levels, and therefore, may not have been able to fully determine the effect of TMAO production on cardiovascular risk. Further studies including randomized, interventional trials that assess TMAO as a risk factor for MACEs are needed to further clarify the link between diet, TMAO levels, and atherosclerotic disease.

## HUMAN GUT MICROBIOME

The interaction between diet and the human gut microbiome in atherosclerotic disease is an area of fervent investigation. As discussed in the section on diet, the gut microbiome is responsible for the production of the pro-atherogenic compound TMA from consumed animal products. Additionally, the human gut microbiome also affects the amount and type

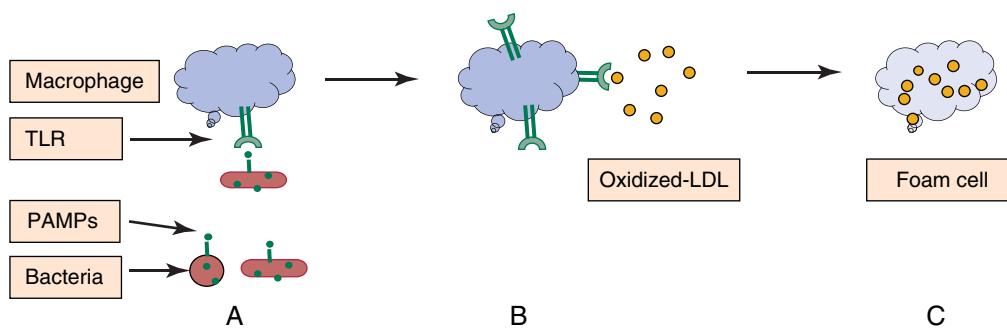


**Figure 16.2** Interaction of Diet and the Human Gut Microbiome. Consumption of meat and animal products lead to microbiome alterations that contribute to obesity and insulin resistance, which cause further alteration of gut microbiome.

of absorbable nutrients derived from the diet.<sup>51</sup> Understanding of variations in human gut microbiome populations is in its initial stages; however, it does seem that certain bacterial phyla are overrepresented in patients with atherosclerotic disease and risk factors compared to patients without atherosclerotic disease. Specifically, there is decreased phylogenetic diversity of gut bacteria and an increased prevalence of Firmicutes relative to Bacteroidetes in obese individuals and those with type-2 diabetes compared to controls.<sup>52,53</sup> Individuals with increased prevalence of Firmicutes are able to produce more absorbable calories for an identical meal than individuals with decreased prevalence of Firmicutes.<sup>51</sup> Additionally, increased prevalence of Firmicutes relative to Bacteroidetes is associated with decreased production of the short-chain fatty acid butyrate and increased production of acetate resulting in inflammation, decreased insulin sensitivity, and obesity.<sup>54</sup> The relationship between obesity, DM, and microbiome profile seems to be bidirectional in that dietary changes and weight loss alter microbiome profiles towards a more “healthy” state consisting of less Firmicutes and alteration of microbiome profile also causes weight loss and increased insulin sensitivity in animal and human studies respectively (Fig. 16.2).<sup>55,56</sup> Larger, prospective and randomized studies with meaningful clinical endpoints are needed before these promising initial investigations into the gut human microbiome can be adopted in the clinical practice setting.

## INFECTION

Efforts to link atherosclerosis with infectious etiologies have spanned decades. Although enthusiasm for an infectious etiology of atherosclerotic disease may have waned after several negative trials of antibiotics, the association and potential



**Figure 16.3** Potential Mechanism of Atherosclerosis Formation by Infectious Pathogens. (A) Pathogen-associated molecular patterns (PAMPs) are recognized by Toll-like receptors (TLRs) on macrophages. (B) Macrophages upregulate TLRs, which can also bind oxidized low-density lipoprotein (LDL). (C) Uptake of oxidized LDL by macrophages causes foam cell formation.

causal link between infectious pathogens and atherosclerosis remains an active area of investigation. Numerous viral and bacterial pathogens have been examined as potential causes of atherosclerosis.

Potential mechanisms by which bacteria and viruses may cause atherosclerosis development include upregulation of adhesion molecules in vascular endothelium and foam cell formation.<sup>57,58</sup> The effect of many pathogens on foam cell formation seems partially dependent on Toll-like receptors (TLRs), which are present on inflammatory cells and bind to bacterial and viral pathogen-associated molecular patterns (PAMPs) as part of the innate immune system. However, they also bind endogenous compounds, such as ox-LDL, and cause macrophages to transform into foam cells (Fig. 16.3).<sup>57-60</sup>

Although the association between atherosclerosis and any single pathogen has been inconsistent, the concept of an increased pathogen burden may better explain the potential link between infection and atherosclerosis. The pathogen burden hypothesis postulates that exposure to an increased number of pathogens creates an increased systemic inflammatory response, which promotes the development of atherosclerosis. This hypothesis is supported by studies demonstrating a higher risk of CAD in patients with antibodies to a larger number of pathogens.<sup>61-64</sup>

## Viruses

### *Herpes Simplex Viruses 1 and 2*

Data linking HSV infection to atherosclerosis are mixed. A meta-analysis of 17 studies investigating the association of HSV-1 and 7 studies investigating HSV-2 seropositivity showed a significant association between both HSV-1 and HSV-2 with atherosclerotic disease. However, there was significant heterogeneity among studies with regard to the populations studied, the definition of exposure and disease outcomes, and the results.<sup>65</sup>

### *Enteroviruses, Hepatitis C, Cytomegalovirus*

The association of cardiovascular events and antibodies to enteroviruses is also inconclusive, with some prospective studies showing a correlation between antibody levels and

cardiovascular events<sup>66</sup> and others studies demonstrating no association.<sup>67,68</sup> Similarly, HCV infection has been shown to be associated with CAD in one study<sup>69</sup> and to have no association with MI in another.<sup>70</sup> The data regarding CMV infection are mainly composed of small case studies, with a meta-analysis of these studies suggesting a modest association between CMV exposure and CAD.<sup>71</sup>

## Bacteria

### *Helicobacter pylori*

*H. pylori* is best known as a cause of peptic ulcer disease, but it has also been associated with atherosclerotic disease. *H. pylori* DNA can be detected in up to 30% of coronary artery atherosclerotic plaques.<sup>72</sup> Its detection in coronary artery plaques by PCR techniques has been criticized for potential false-positive rates, but use of the internal mammary arteries as a control has lessened this concern.<sup>72</sup> *H. pylori* has been associated with increased risk of CAD, MI, and stroke, with the more virulent CAG A strains possibly conferring the highest risk.<sup>73-77</sup> The association of *H. pylori* infection with decreased HDL levels and increased HbA<sub>1c</sub> levels provides a possible mechanistic link between *H. pylori* infection and atherosclerosis.<sup>78,79</sup> However, the data are inconsistent, with several large studies not demonstrating a positive association between seropositivity to CAG A-positive *H. pylori* and cardiovascular mortality.<sup>61,80</sup> Inconsistent results may stem from variability in classifying exposure, disease endpoints, and confounding factors such as past and present socioeconomic status.<sup>81</sup>

### *Chlamydia pneumoniae*

Many case-control<sup>82-85</sup> and a few prospective<sup>86,87</sup> studies have suggested an association between seropositivity or high serum titers to *C. pneumoniae* and atherosclerotic heart disease and ischemic stroke. However, other large prospective cohort trials have failed to show an association between seropositivity to *C. pneumoniae* in healthy individuals and the subsequent development of cardiovascular events.<sup>87,88</sup> Differences in the definition of exposure, definition of outcomes, and duration of follow-up in prospective trials may explain some of the differences between these trials.

Despite the possible association between *C. pneumoniae* infection and subsequent atherosclerosis, causation has been difficult to prove. The use of antibiotics effective against *C. pneumoniae*, such as azithromycin<sup>87,89–93</sup> or gatifloxacin,<sup>94</sup> has not shown any benefit in the secondary prevention of cardiovascular events. The largest of these trials, totaling almost 16,000 patients, had mean follow-up times of 2.0 to 3.8 years and included a fairly lengthy antibiotic regimen that continued for 1 to 2 years.<sup>92–94</sup> However, there may be a benefit in decreasing secondary cardiovascular event rates using broader antibiotic regimens of either azithromycin and metronidazole or amoxicillin and metronidazole<sup>95</sup> and in preventing the progression of carotid plaque using roxithromycin.<sup>96</sup> Interestingly, the benefit of using antibiotics to lower cardiovascular event rates appears to be independent of seropositivity to *C. pneumoniae*, suggesting that additional pathogens or mechanisms may be involved.<sup>95</sup>

### Oral Pathogens

Oral pathogens have received substantial interest as a potential cause of atherosclerosis development and progression. Oral bacteria are detected in the blood after normal daily activities such as tooth brushing and therefore have access to the systemic circulation. There is a strong association between periodontitis and clinical atherosclerosis. Periodontitis is associated with an increased risk of MI, ischemic stroke, and peripheral arterial disease.<sup>97–103</sup> Patient-specific oral bacteria have also been detected in and cultured from coronary atherosclerotic plaques.<sup>104</sup>

The relationship between oral pathogens and atherosclerosis appears to depend more on the entire oral microbiome rather than any specific pathogens, with an increasing number of oral pathogens exerting a synergistic effect on atherosclerosis development.<sup>64</sup> However, although the association between periodontitis and atherosclerosis is well established, causality is not clear.

The benefit of treating periodontitis with regard to cardiovascular events has been inferred through changes in cardiovascular disease biomarkers, such as C-reactive protein (CRP) levels, but not demonstrated through decreases in clinical endpoints, such as MI or stroke. Results of individual trials are mixed, with some showing no benefit in CRP and interleukin-6 (IL-6) reduction<sup>105,106</sup> whereas others demonstrate CRP and IL-6 reductions with periodontal therapy regimens.<sup>107,108</sup> Reductions in CRP levels occur regardless of whether antibiotics are added to the mechanical treatment of periodontitis, but the two modalities may exert synergistic effects.<sup>107,109,110</sup> Finally, the PAVE study<sup>111,112</sup> evaluated the effect of periodontal treatment on secondary prevention of cardiovascular events. This study did not show any benefit in CRP levels or cardiovascular event rates from treatment of periodontitis. However, a large portion (48%) of the “control group” also received treatment for periodontitis, and the treatment arm sustained only a short-term, modest improvement in the participants’ periodontal disease status. Therefore, despite the association between periodontitis and atherosclerosis, it is not yet known whether periodontitis causes atherosclerosis or if treatment of periodontitis will decrease major adverse cardiac events.

## ENVIRONMENTAL TOXINS

### Persistent Organic Pollutants

Emerging evidence suggests that some long-lasting environmental toxins, collectively known as POPs, are associated with both atherosclerosis and type II DM. POPs include many industrially produced compounds such as herbicides and dioxins. The toxic effects of 2,3,7,8-tetrachlorodibenz o-p-dioxin (TCDD), the dioxin contaminant in the Agent Orange herbicide used during the Vietnam War, are well characterized, and the toxic effects of all other dioxins are expressed in relation to that of TCDD. TCDD is found as a by-product of industrial waste incineration, a contaminant in herbicides, and a by-product of pulp and paper mills and metal production.<sup>113</sup> Dioxins are highly lipophilic substances that accumulate in the fat stores of animals and humans due to their long biological half-lives of 7 to 11 years.<sup>114,115</sup> Polychlorinated biphenyls (PCBs) are another well studied class of POPs with similar mechanism of action and disease associations as dioxins.

The National Academy of Science, Engineering and Medicine routinely examines evidence linking POPs to diseases, including ischemic heart disease, stroke, and type II DM. In 2000 this institution’s report on veterans and Agent Orange exposure stated that there is “limited or suggestive” evidence of an association between these chemicals and type II DM, ischemic heart disease, hypertension, and stroke. Subsequent updates of this report at 2-year intervals have upgraded the evidence of association between Agent Orange and hypertension to “sufficient” and upheld the remaining conclusions.<sup>116</sup>

More recent studies have also supported the association between POP exposure, atherosclerotic disease, DM II, ischemic stroke and metabolic syndrome. Both estimated exposure and blood level concentrations of POPs are associated with type II DM and serum glucose abnormalities in military veterans. Many studies of civilian populations also show an association between occupational and environmental exposure to POPs and DM, although other studies show mixed results or no such association.<sup>117–132</sup>

The aryl hydrocarbon receptor (AhR) is the most studied mediator of the proposed mechanism by which POPs exposure exerts toxic effects, including the development of type II DM. POPs can bind the AhR and cause downstream effects affecting the regulation of the cell cycle and promoting inflammation. There is also an AhR-independent pathway that affects results in the upregulation of inflammatory mediators by altering intracellular concentrations of calcium ions.<sup>133,134</sup> Another mechanism by which some POPs may contribute to atherosclerosis is via the upregulation of flavin monooxygenase-3 (FMO3), the hepatic enzyme responsible for producing the proatherogenic compound TMAO from dietary precursors (see Diet, above). Exposure to some POPs has recently been shown to cause upregulation of FMO3 as well as increased TMAO production in response to PC supplementation,<sup>135</sup> indicating that diet and environmental contaminants may synergistically lead to atherosclerotic disease (see Fig. 16.1).

## Heavy Metals

Heavy metals are another source of environmental contaminants that may negatively affect cardiovascular health and promote atherosclerosis. Activities such as the burning of coal, municipal waste incineration, smelting, and the production of paper have led to the accumulation of arsenic, cadmium, and mercury in the environment.

### Arsenic

The contamination of drinking water with arsenic is a major problem in the developing world. Blood arsenic levels are associated with multiple atherosclerotic risk factors, such as DM II and hypertension. Initially, only high levels of exposure and prolonged exposure times were associated with DM II<sup>136</sup>; however, arsenic seems to be associated with DM II even at “low” levels of 50 to 100 µg/L in drinking water.<sup>137,138</sup> There is also an association between levels of arsenic in blood and urine and hypertension (HTN).<sup>118,139,140</sup> Exposure to arsenic is also linked with coronary artery disease, stroke, and PAD.<sup>141</sup> The World Health Organization and United States Environmental Protection Agency now recommend arsenic levels of less than 10 µg/L, with some studies showing continued associations between arsenic ingestion and cardiovascular mortality even below these levels.<sup>142</sup>

### Cadmium

Cadmium exposure can occur through the ingestion of contaminated vegetables or smoke inhalation. The association of between cadmium exposure and tobacco smoke had previously made it difficult to determine whether cadmium exposure is linked with atherosclerosis independent of exposure to tobacco.<sup>143</sup> However, subsequent studies have demonstrated that cadmium exposure is associated with an increased incidence of MI, stroke, CAD, and PAD independent of smoking status.<sup>144,145</sup>

Cadmium levels may also affect the progression of atherosclerotic plaques, with higher cadmium levels being associated with the progression of carotid atherosclerosis.<sup>146,147</sup> High levels of cadmium in symptomatic carotid plaques and the association between cadmium levels and the increased density of macrophages in carotid plaques has led some investigators to suggest that cadmium exposure can affect plaque stability and increase the incidence of ischemic stroke.<sup>148,149</sup> The association between cadmium exposure and atherosclerotic disease may be more pronounced in women than in men.<sup>144,146</sup> Potential mechanisms by which cadmium exposure can lead to atherosclerosis may include disruption of vascular endothelial integrity and endothelial cell junctions<sup>150,151</sup> as well as free-radical production and the depletion of endogenous free-radical scavengers.<sup>152,153</sup>

### Mercury

Mercury vapor from the burning of fossil fuels, waste incineration and other industrial causes is eventually deposited in lakes, rivers, and oceans, where it can be converted to organic

methyl mercury. Methyl mercury bioaccumulates in aquatic life, especially large predatory fish, such as shark, swordfish, and tuna.<sup>154</sup> The protective effect of fish consumption on cardiovascular health due to omega-3 polyunsaturated fatty acids, has the potential to obscure some of the detrimental effects of exposure to organic mercury. However, a large, prospective study of a Finnish population has demonstrated a strong association between levels of mercury in hair and MI and death from CAD at 6-, 10-, and 14-year follow-up intervals.<sup>155–157</sup> In addition, mercury appears to attenuate the protective effect of omega-3 fatty acids on the incidence of MI.<sup>156,157</sup> However, not all studies have corroborated the association between mercury levels and CAD.<sup>158–160</sup>

## Air Pollution

Air pollution from automobiles and industrial production consists of free radicals, reactive aldehydes, and particulate matter. The association between air pollution, atherosclerosis, and atherosclerotic risk factors is controversial. There are methodologic challenges, such as quantifying the length and intensity of pollution exposure, accounting for confounders, and determining the true rates of outcomes. However, overall, multiple studies suggest an association between air pollution and the development of DM II.<sup>161–167</sup> In addition, the association between air pollution exposure and DM may be exaggerated in women and nonsmokers.<sup>160,162,166</sup> Increased exposure to air pollution is associated with increased levels of high-sensitivity CRP (hsCRP) and other inflammatory markers,<sup>168–170</sup> as well as an increased prevalence of coronary artery disease, stroke, ischemic heart disease, and congestive heart failure.<sup>161–170</sup>

Multiple theories exist regarding potential mechanisms by which air pollution can cause atherosclerosis. Animal and human studies on the effects of air pollution demonstrate increased markers of systemic inflammation, insulin resistance, and activation of the innate immune system through the activation of TLRs.<sup>171–175</sup> Free-radical stress from air pollution may also cause mitochondrial dysfunction and lead to atherosclerosis through increased intracellular oxidative stress, mutations in mitochondrial DNA, and decreasing metabolic rates.<sup>173</sup>

## SUMMARY

There continues to be progress in understanding atherosclerosis and its risk factors. The behavior of the atherosclerotic lesion, the role of various cells within the atherosclerotic lesion, and the effect of hyperlipidemia are more complex than previously demonstrated. Many less commonly considered factors such as environmental exposures and the interplay between diet and the gut microbiome may also contribute to atherosclerotic disease. As our understanding of the links between diet, infection, environmental exposures, and traditional atherosclerotic risk factors expands, there will be opportunities to develop new therapies and preventive strategies through improved pharmacotherapy and public health measures.

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A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com).

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# International and Ethnic Trends in Vascular Disease

LIDIE LAJOIE and SUBODH ARORA

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The 21st century has ushered in a number of changes in the distribution of vascular disease worldwide, primarily due to demographic changes and trends in atherosclerotic risk factors. These global trends require concerted efforts at the patient, provider, and public health level to adequately care for the increasing burden of vascular disease worldwide. Similarly, significant advancements in the understanding of ethnic differences in the epidemiology of vascular disease, delivery of care, and outcomes of treatment modalities have also been made in the past decade. The disparities identified have prompted the development of a number of strategies to improve the care of the diverse population of patients with vascular disease.

## **INTERNATIONAL TRENDS**

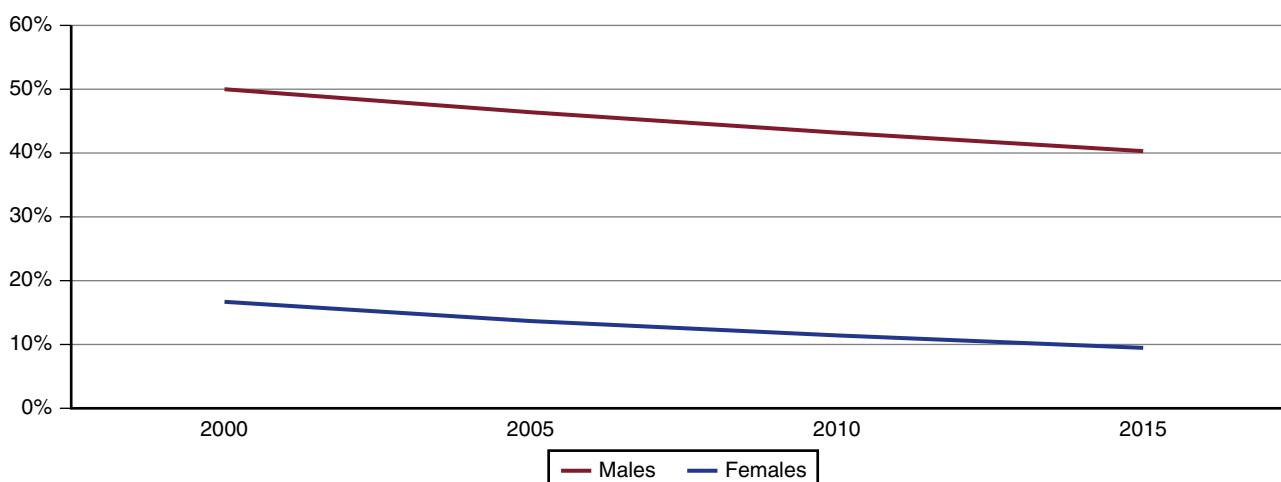
Globally, atherosclerosis is a leading cause of vascular disease, including ischemic heart disease (IHD), ischemic stroke, and peripheral arterial disease (PAD). Based on large-scale population-based studies, there is an increased burden of disease resulting primarily from the increasing trends of risk factors of atherosclerosis, primarily smoking and diabetes. A multifaceted approach including environmental and legislative interventions for health promotion, primary intervention, and access to affordable evidence-based evaluation and treatment of major risk factors is required to combat the growing burden of vascular disease worldwide.

## **Risk Factors**

### *Tobacco Use*

There are currently more than 1 billion smokers worldwide.<sup>1</sup> Fortunately, the global prevalence of daily tobacco use has declined over the past 30 years but varies by gender and region (Fig. 17.1).<sup>2</sup> Men smoke more than women in all regions, with the largest disparity between the genders in the Western Pacific region and lowest in the European region. The highest smoking prevalence is in Southeast Asia, with nearly 50% daily tobacco use, followed by the European region, the Western Pacific (including China), the Eastern Mediterranean region, the Americas, and Africa.<sup>1</sup> The last quarter of the 20th century saw an increase in smoking in a number of developing regions, including parts of Latin America, the Eastern Mediterranean, and Southeast Asia.<sup>3</sup> As a result of global public health efforts initiated at the turn of the century, there was a worldwide trend toward decreased prevalence of tobacco use in the first two decades of the 21st century, from one-third of the global population using tobacco in 2000 to one-fourth by 2020. These trends toward tobacco abstinence are demonstrated in males and females, and across all global regions, with the greatest reduction in tobacco use in the last two decades seen in Southeast Asia, particularly among females in that region.<sup>1</sup>

More than 8 million people die from tobacco use and exposure each year.<sup>1</sup> Smoking is estimated to cause nearly 10% of cardiovascular deaths worldwide. The highest proportion

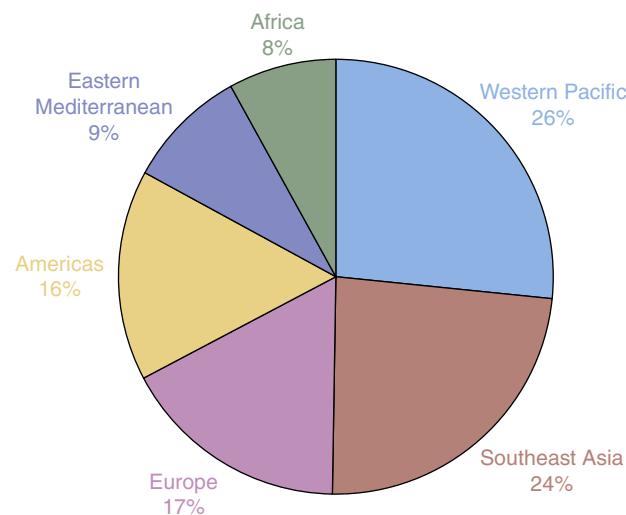


**Figure 17.1** Trends in Global Prevalence of Current Tobacco Use by Gender, 2000–2015.

of cardiovascular deaths attributed to smoking is observed in North America (22%), Eastern Europe (17%), Western Europe (13%), and Southeast Asia (10%). Based on gender, the effects on men have demonstrated a relative risk of 1.6 for IHD mortality and 1.6 for stroke mortality among current smokers compared with never-smokers.<sup>4</sup> Among women, current smokers were found to have 3 times the risk of mortality from IHD, 3 times increased risk of stroke mortality, and 6 times increased risk of death from aortic aneurysm compared with never-smokers.<sup>5</sup> Looking forward, it is expected that the countries with both the highest smoking prevalence rates and high consumption rates (>20 cigarettes per day) will likely face the greatest health consequences among current smokers: China, Greece, Ireland, Italy, Japan, Kuwait, Korea, Philippines, Uruguay, Switzerland, and Russia.<sup>2</sup>

### Diabetes

The global epidemic of diabetes is expanding as rapidly growing populations, particularly in India and China, adopt Western lifestyles. These studies projected that the number of adults worldwide with diabetes will more than double from 2000 to 2030 due to the combined forces of improved survival from communicable diseases, abundance of food, and less physically demanding lifestyles.<sup>6</sup> The International Diabetes Federation estimates that globally 415 million people had diabetes in 2015, and this figure is expected to rise to 642 million by 2040.<sup>7</sup> By 2017 an estimated 10% of adults older than 25 years were living with diabetes worldwide,<sup>8</sup> with the highest prevalence in the Eastern Mediterranean and Americas regions and lowest in Africa and the Western Pacific Regions<sup>9</sup> (Fig. 17.2). Population growth and aging alone accounted for 70% of the 198 million new cases of diabetes between 1980 and 2008.<sup>2</sup> In the next few decades, the regions that are projected to experience the highest growth rates in the number of persons with diabetes are the Eastern Mediterranean and Africa regions.<sup>7</sup> In 2017 alone, nearly 1.4 million deaths were attributed to diabetes globally.<sup>9</sup> Large-scale meta-analysis of prospective observational studies quantified that diabetes mellitus increases



**Figure 17.2** Prevalence of Diabetes Mellitus by World Health Organization Regions, 2017.

vascular mortality rates by a factor of 2.<sup>10</sup> Therefore these regions with the greatest increase in diabetes prevalence can also anticipate an associated increase in vascular morbidity with its associated costs as the population ages.

### Ischemic Heart Disease

IHD has a worldwide prevalence of 5%–8%.<sup>11</sup> Globally, the age-standardized incidence of acute myocardial infarction (AMI) and prevalence of angina and ischemic heart failure decreased from 1990 to 2010. Regionally, the greatest decline in age-standardized incidence of AMI during this period was observed in Australasia, Western and Central Europe, and North America high-income regions. However, Eastern Europe was noted to go against the trend of worldwide decline in age-standardized incidence of AMI, demonstrating an increased incidence of 62 per 100,000 in males and 17 per 100,000 in females during this time period.<sup>12</sup>

IHD is the leading cause of death from noncommunicable diseases worldwide. In 2017 the highest mortality rates from IHD were reported for Eastern Europe (including Russia) and Central Europe, with these regions demonstrating more than 10 times the mortality rate observed in the regions with the lowest rates: Eastern and Western Sub-Saharan Africa.<sup>10</sup> In the last decade the Eastern European region has seen a reversal of the trend of increased IHD mortality, with a steadily decreasing mortality rate from IHD despite increasing prevalence rate over the same time period,<sup>9</sup> attributable to improvements in treatment.<sup>13</sup>

## Cerebrovascular Disease

In 2017, the World Health Organization estimated a worldwide incidence of 11.9 million strokes per year, with the greatest incidence in populations of the Western Pacific (5.2 million), East Asia (4.4 million), and Europe (2.1 million).<sup>9</sup> The global trend in age-standardized incidence of stroke indicated a decrease from 1990 to 2010 by 12% in high-income countries (HICs) but suggested an increase of the same degree in low- and middle-income countries (LMICs).<sup>14</sup>

Stroke is the second leading cause of death worldwide. Stroke-related mortality and disability-adjusted life-years (DALYs) lost also increased over the past two decades, with most of the burden in LMICs. These trends are represented in Figure 17.3. Age-adjusted mortality rates for stroke decreased significantly globally and in both high-income and low- and middle-income regions. This discrepancy between rising absolute numbers of stroke mortality and decreasing age-adjusted mortality rates for stroke globally can be explained by a 36% decrease in stroke-related mortality among persons older than 75 years.<sup>14</sup> Measures to improve stroke prevention and care (i.e., smoking cessation programs, blood pressure control, acute stroke units) that have been adopted in HICs are the most likely explanation for the decreasing incidence and mortality rates observed in the past 20 years. In countries like China, Russia, and India, with very high stroke-related mortality attributable to tobacco use, even a modest reduction in the number of current smokers could prevent millions of deaths.<sup>15</sup>

## Peripheral Arterial Disease

Lower extremity PAD, including intermittent claudication and critical limb ischemia, is the third leading cause of atherosclerotic vascular morbidity after IHD and stroke. Globally, more than 200 million people are living with PAD, with more than two-thirds of these persons residing in LMICs.<sup>16</sup> In the past decade the number of people with PAD has increased both in HICs by 17%, and LMICs by 36%.<sup>9</sup> The regions with the highest incidence of PAD as of 2017 were the Western Pacific and Southeast Asia, LMICs, whereas the lowest numbers of people living with PAD were in the Eastern Mediterranean and Africa regions (Fig. 17.4). The increase in PAD prevalence over the past decade was highest in the elderly, thereby suggesting the global prevalence of PAD will grow rapidly, because of an aging world population and increased prevalence of atherosclerotic risk factors, particularly smoking and diabetes.

In addition, PAD, as opposed to IHD and stroke, has a lower associated mortality, accounting for only 1% to 2% of cardiovascular deaths globally each year.<sup>10</sup> The high-income regions of Europe and the Americas have consistently demonstrated the highest regional mortality rates from PAD (Fig. 17.5).<sup>9</sup>

These trends pose a significant public health challenge in LMICs due to both the rapid rise in prevalence of PAD on healthcare resources and the dependence of the population on walking substantial distances for activities of daily living.<sup>16</sup> The limited availability of healthcare services in these regions is predicted to lead to a significant number of limb amputations with their associated social needs in the coming decades.

## Aortic Aneurysm

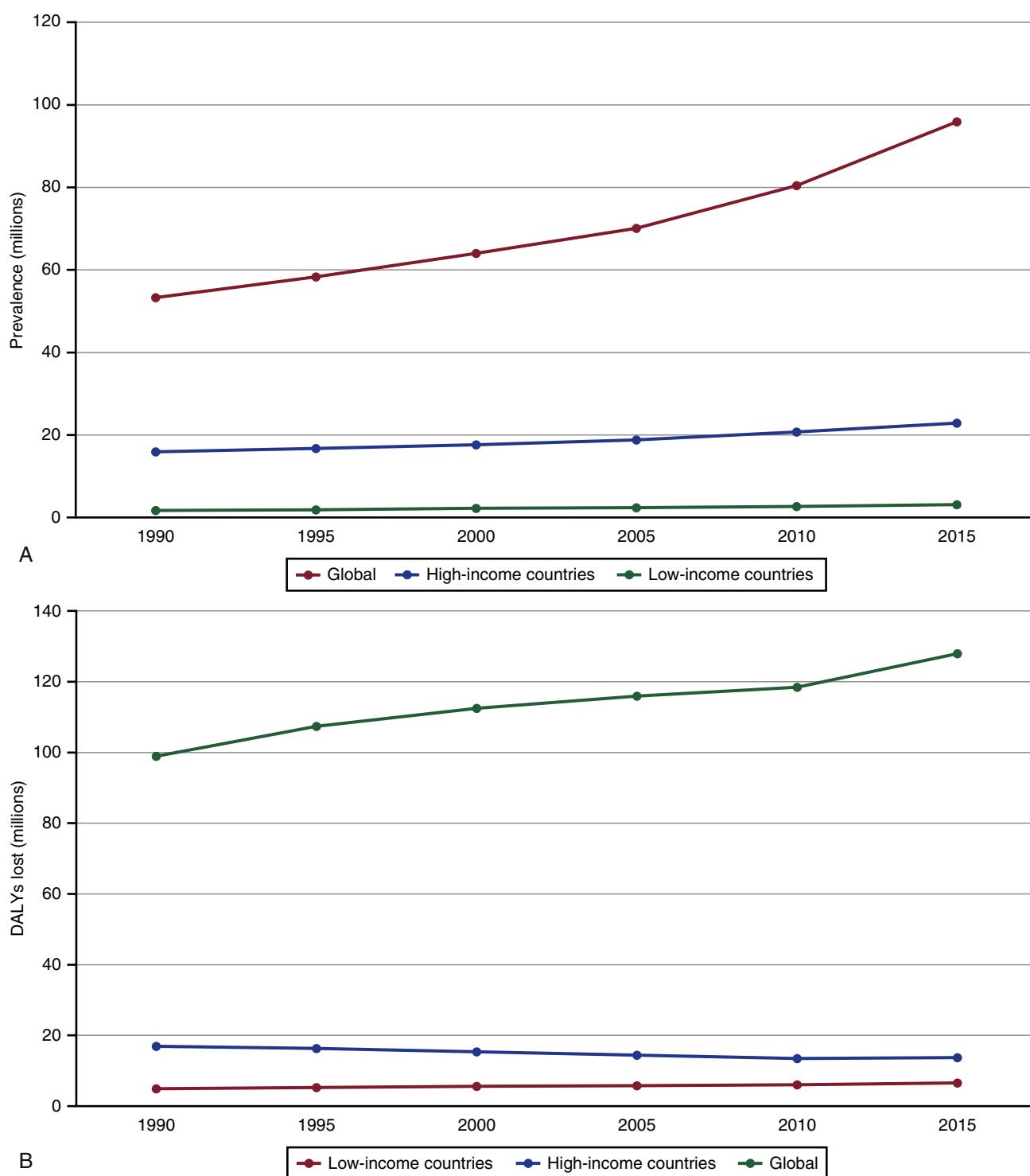
A consistent increase in the incidence and mortality from both thoracic and abdominal aortic aneurysm (AAA) were noted in many HICs during the second half of the 20th century, with a prevalence estimated at 5% by the turn of the century.<sup>17</sup> In 1990 to 2010 the highest global prevalence was in Australasian and North American high-income regions despite a decrease of prevalence over the past 20 years, whereas Oceania, tropical Latin America, Asia Pacific HICs, Central Asia, South Asia, and the Sub-Saharan African regions all demonstrated an increase in aortic aneurysm prevalence.<sup>17</sup>

Despite a net decline in the global prevalence of aortic aneurysm, mortality rates have increased worldwide over the same time period: from 2.49 per 100,000 in 1990 to 2.78 per 100,000 in 2010.<sup>18</sup> The highest mortality rates from aortic aneurysms have been consistently observed in the Australasia and Western Europe regions over the past few decades<sup>18</sup>; however, other studies have documented a decline in mortality rates in many HICs, likely due to a combination of comprehensive tobacco use reduction efforts and implementation of targeted screening programs.<sup>17,19</sup>

## Global Strategies

A number of strategies have proven effective in decreasing the global burden of vascular disease. Public health measures to treat hypertension, high cholesterol, and diabetes and reduce smoking can further reduce the burden of IHD, cerebrovascular disease, PAD, and aortic aneurysm disease.

Interventions that are highly cost-effective, feasible, and culturally acceptable to reduce tobacco use include increases in prices of tobacco products, policies designating smoke-free work and public spaces, mass media campaigns providing education about tobacco dependence and health effects, and bans on tobacco advertising, promotion, and sponsorship. The cost of implementation of these interventions is estimated at less than \$0.50 per capita and has been effective when implemented; however, only 180 countries have ratified the WHO Framework Convention on Tobacco Control (Table 17.1). Between 2007 and 2014 there was a significant increase in the proportion of countries that have implemented these tobacco use reduction measures. Over this time period, in countries



**Figure 17.3** Trends in Global Burden of Stroke, 1990 to 2015. (A) Prevalence rate (per 100,000 people). (B) Disability-adjusted life-years (DALYs) lost.

that implemented these measures, a 1.57% reduction in tobacco use prevalence per measure was demonstrated.<sup>20</sup>

Several evidence-based interventions for the management of diabetes have proven cost-effective while improving health<sup>8</sup> and are reviewed in Chapter 12.

Approaches to improve cardiovascular health globally can be categorized as policy strategies, provider-level

interventions, or patient-level interventions (Table 17.2). Primary prevention of atherosclerotic disease with a regimen of aspirin, statin, and blood pressure-lowering agents may significantly reduce the risk of mortality in people at high cardiovascular risk for a modest cost. In high-risk patients between 40 and 70 years of age, providing this regimen has been estimated to avert approximately 20% of cardiovascular

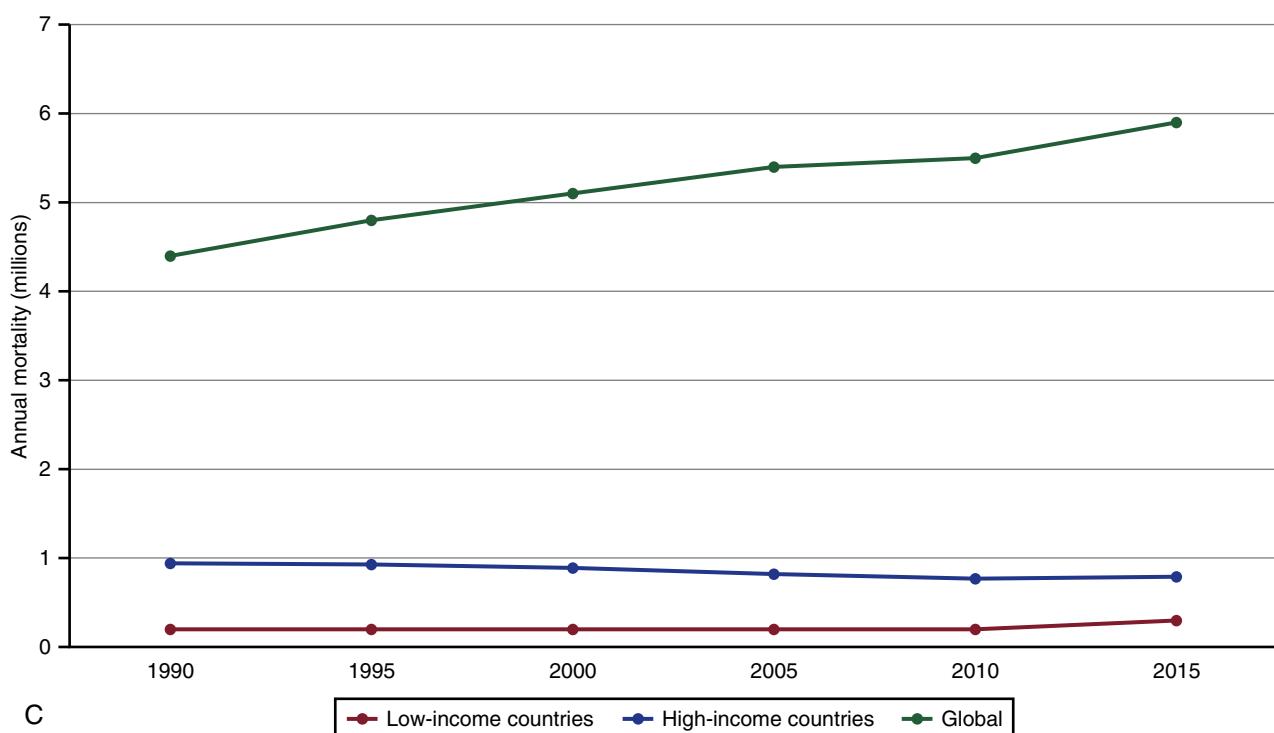


Figure 17.3 Cont'd (C) Annual mortality.

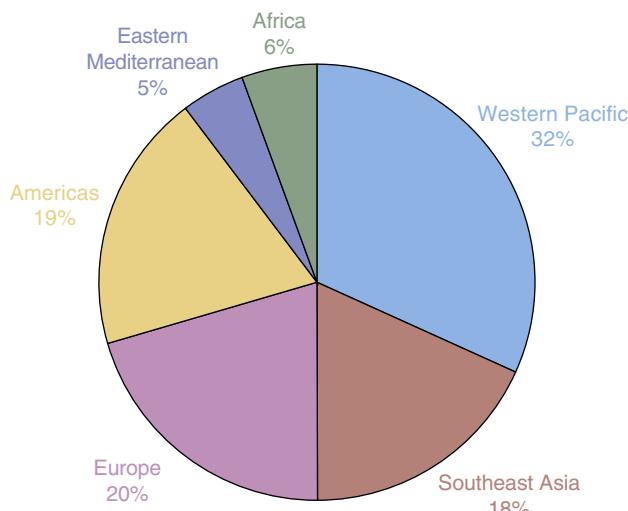


Figure 17.4 Prevalence of Peripheral Arterial Disease by World Health Organization Regions, 2017.

deaths over 10 years at a cost of less than \$1 per person in low-income countries and less than \$3 per person in middle-income countries.<sup>8</sup>

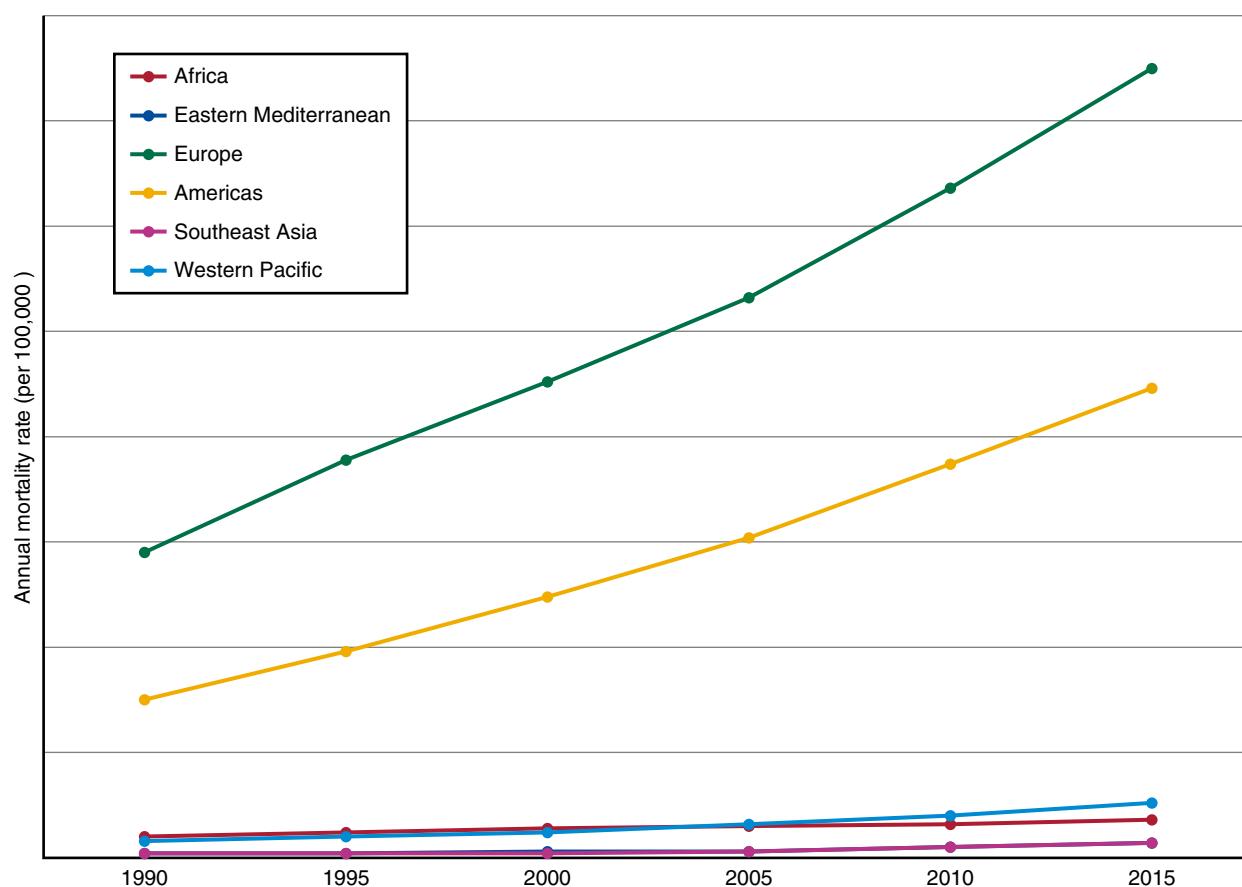
## ETHNIC TRENDS

Current demographic trends in the United States indicate that significant changes are occurring in the proportion of racial/ethnic groups represented in the overall population. Compared with estimates in 2000, the proportion of Whites is expected to decrease, while proportions of Hispanics and Asians will nearly double by 2050 (Fig. 17.6).<sup>21</sup>

## Trends in the Risks for Cardiovascular Disease

Racial and ethnic trends in the risk factors for and occurrence of cardiovascular and related diseases in the United States have been documented in the past few decades, and provide insights in the morbidity and mortality that can be expected in the years to come. It is important to note that the major broad racial/ethnic categories used to describe populations (White, Black, Hispanic, Asian) represent genetically heterogeneous groups of diverse origins in these broad categories, resulting from migration and genetic intermixing. Rather than genetic factors, it is the psychosocial factors, particularly nutritional behaviors and disparities in access and delivery of healthcare, that have the most powerful effect on trends of vascular disease within these racial/ethnic constructs. Notable differences in cardiovascular risk factors – obesity, diabetes, hypertension, hypercholesterolemia, and smoking – have all been described.

The epidemic of obesity in the United States is not distributed equally among racial/ethnic groups. The highest obesity rates ( $BMI \geq 30 \text{ kg/m}^2$ ) are seen among non-Hispanic blacks (49.6%) and Hispanics (44.8%), followed by non-Hispanic whites (42.2%), whereas Asians have been much less affected (17.4%).<sup>22</sup> A parallel trend is seen in the age-adjusted prevalence of diabetes, which has risen at a similar rate in all racial/ethnic group categories (Fig. 17.7).<sup>23,24</sup> Trends for Asians may not accurately predict diabetes because the cutoff points of BMI indicating high risk for hypertension, dyslipidemia, and cardiovascular morbidity are lower than for other groups (obesity defined as  $BMI = 27.5 \text{ kg/m}^2$  for Asians).<sup>25</sup> However, after adjusting for age, gender, and BMI, Asians are 60% more likely to have diabetes than Whites.<sup>26</sup>



**Figure 17.5** Trends in Mortality Rates Attributed to Peripheral Arterial Disease by Geographic Regions, 1990 to 2015.

**TABLE 17.1** WHO Framework Convention on Tobacco Control

**Price and Tax Measures to Reduce the Demand for Tobacco**

- Tax increases that result in an increase of the sales price of tobacco products
- Prohibition or restriction of sales of tax- and duty-free tobacco products

**Nonprice Measures to Reduce the Demand for Tobacco**

- Comprehensive smoke-free policies to provide protection from exposure to tobacco smoke in indoor workplaces, public transport, and indoor and other public spaces
- Regulation of the contents and emissions of tobacco products and the methods by which they are tested and measured
- Disclosure of the constituents and emissions of tobacco products by manufacturers and importers
- Requirement that tobacco product packaging carry large health warnings and messages describing the harmful effects of tobacco (constituting more than 50% of the principal display areas)
- Education, communication, training, and public awareness campaigns
- Comprehensive ban on all tobacco advertising, promotion, and sponsorship
- Provision of support for reducing tobacco dependence and cessation, including counseling, psychological support, nicotine replacement, and education programs

**Measures to Reduce the Supply of Tobacco**

- Elimination of illicit trade in tobacco products by marking of tobacco packaging to enable tracking and tracing, monitoring of cross-border trade, and confiscation of proceeds derived from illicit trade in tobacco products
- Prohibition of sales of tobacco products to children and limitation of access of underage persons to tobacco products through elimination of distribution of free tobacco products, tobacco vending machines accessible to minors, and the sales of tobacco products individually or in small packets

**TABLE 17.2****Comprehensive Strategy to Address Cardiovascular Disease<sup>a</sup>****Policy Approaches (Global, National, Local)**

- Comprehensive tobacco control policies
- Food, agricultural, and trade policies that promote consumption of fruits and vegetables
- Environmental policies to limit meat, dairy, and palm oil production
- Urban planning policies to promote active transport to work and leisure-time activity

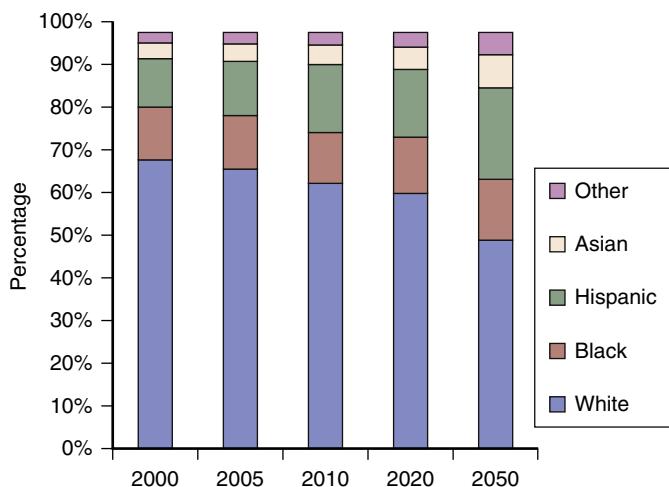
**Healthcare Delivery – Provider-Level Approaches**

- Creation of systemic infrastructure by establishment of disease management programs
- Adherence to clinical practice guidelines, with audit and feedback mechanisms to improve quality of care

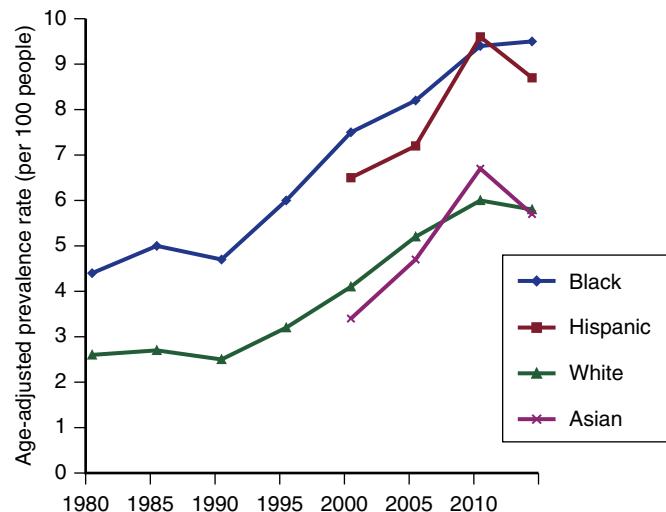
**Healthcare Delivery – Patient-Level Approaches**

- Registration, recall, reminding, reinforcing, and review of patients with linked, simplified, stepped-care algorithms
- Fixed-dose combination or polypill therapy to increase adherence to multidrug regimen

<sup>a</sup>Modified from Huffman MD. Cardiovascular health in low- and middle-income countries. *Curr Probl Cardiol.* 2014;39:399–419.

**Figure 17.6** Percentages of Projected US Population by Race/Ethnicity.

The National Health and Nutrition Examination Survey (NHANES) noted an 18% relative increase in age-standardized prevalence rate of hypertension between the 1988–1994 survey and the 1999–2004 survey, with highest rates among Blacks and lowest rates among Hispanics at both time points.<sup>27</sup> This disparity continued in the 2017–2018 survey<sup>28</sup> (Fig. 17.8). Increases in BMI accounted for nearly all of the increase in hypertension in men, and much (but not all) of the increased prevalence in women. Greatest relative increases in prevalence rates were observed among White and Black women. Among Whites, awareness, treatment, and control of hypertension have improved significantly among men but not women between the survey periods. Blacks had the highest awareness

**Figure 17.7** Racial/Ethnic Trends in Age-Adjusted Rates of Diagnosed Diabetes per 100 Persons in the United States, 1980 to 2014.

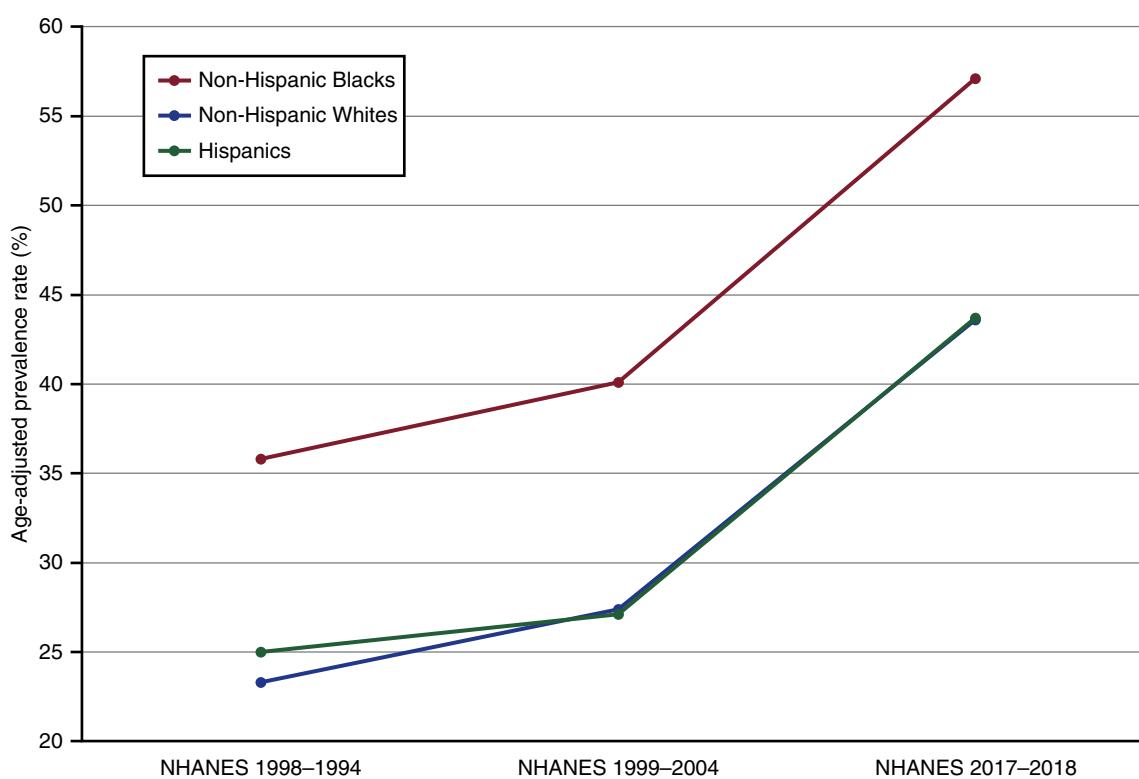
and treatment rates in both surveys, and significant improvements were noted in both measures between the two time periods. However, rates of hypertension control among Blacks have consistently lagged behind those of Whites. Hypertension awareness, treatment, and control have been consistently lowest among Hispanics, and no demonstrable reductions in this disparity has been made from 1988 to 2012.<sup>29</sup>

NHANES has also tracked the prevalence of hypercholesterolemia among whites, blacks, and Hispanics and found that within these groups there has been no significant change in differences from 1999 to 2016. The age-adjusted prevalence of hypercholesterolemia in NHANES was highest for Whites, at 13%, and similar for Hispanics (11.2%), Asians (10.8%) and Blacks (10.5%).<sup>30</sup> However, significant disparities existed in that Blacks and Hispanics were less likely than Whites to have had their cholesterol checked by their doctor, and if laboratory values demonstrated hypercholesterolemia, these groups were less likely to report having been told by a healthcare provider that they had high cholesterol, leading to substantially lower rates of treatment and control. Once told about their hypercholesterolemia, Blacks, Whites, and Hispanics were equally likely to report use of cholesterol-lowering medication.<sup>31</sup>

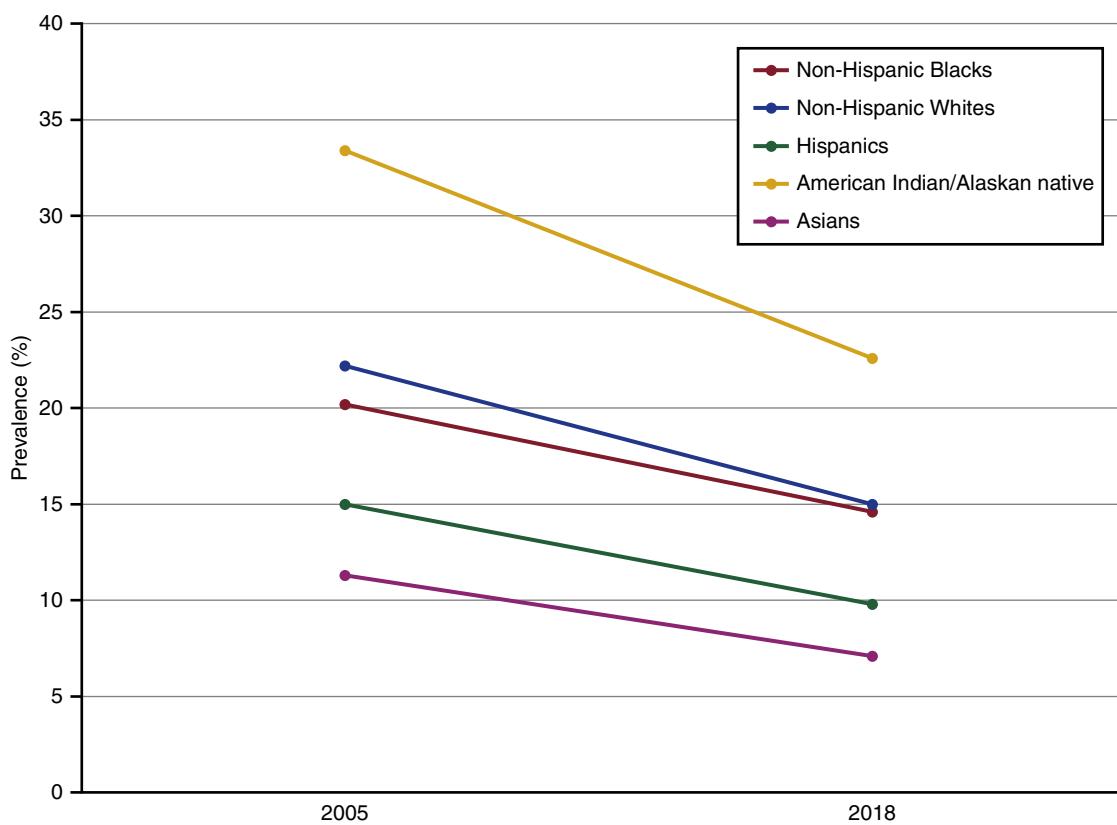
Cigarette smoking has declined among US adults overall but still remains quite prevalent among American Indian/Alaska Natives (23%) (Fig. 17.9).<sup>32</sup> Blacks and Whites demonstrate similar rates of tobacco use and decline in prevalence. Despite studies suggesting that Hispanic smokers are half as likely as Whites to be advised on or offered assistance with smoking cessation,<sup>33</sup> the largest reduction in smoking prevalence by racial/ethnic group has been seen among Hispanics and Asians.<sup>34</sup>

**Cerebrovascular Disease**

Stroke is a leading cause of death and disability in the United States,<sup>35</sup> with the highest age-adjusted prevalence in Blacks (3.9%) compared with Hispanics (2.5%) and Whites (2.5%).<sup>33</sup> A number of studies have suggested that there is a decreased



**Figure 17.8** Racial/Ethnic Trends in Age-Adjusted Prevalence Rates of Hypertension in the United States, The National Health and Nutrition Examination Survey (NHANES).



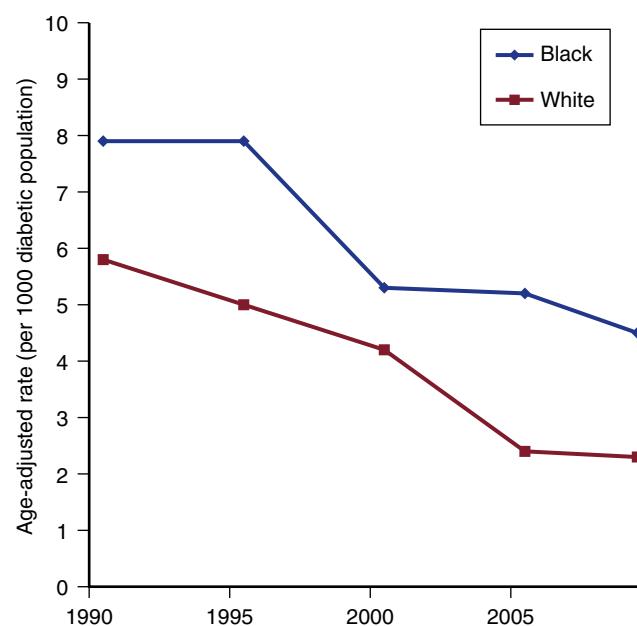
**Figure 17.9** Racial/Ethnic Trends in Prevalence of Adult Cigarette Smokers in the United States, 2005 to 2018.

utilization of surgical and nonsurgical interventions, as well as worse outcomes following these interventions, among racial/ethnic minority groups. African Americans with acute ischemic stroke are less likely to be admitted to centers of excellence for stroke care.<sup>36</sup> The utilization of mechanical thrombectomy for acute stroke is lower among Blacks and Hispanics as compared to Whites.<sup>37</sup> The disparity in treatment of high-grade extracranial carotid artery stenosis with carotid endarterectomy is greatest for Asians compared with Whites, where the ratio of intervention in Asians/Whites is 0.08, whereas the Hispanic/White disparity ranges from 0.06 to 0.28, and the Black/White ranges from 0.36 to 0.39.<sup>35</sup> These differences may result from unmeasured differences in patient preferences or disparities in access to care, the latter of which is substantiated by two large prospective cohort studies of racial/ethnic differences in carotid endarterectomy rates within the VA healthcare system (an equal access system). These studies did not find evidence of racial disparities in carotid endarterectomy (CEA) use rates.<sup>38,39</sup> Negative outcomes after carotid endarterectomy have also disproportionately affected Blacks and Hispanics, because studies have reported a higher rate of postoperative stroke and death in Blacks and Hispanics compared with whites.<sup>40–43</sup> Limited access to optimal surgical care may play a role in these racial/ethnic differences in outcomes after carotid endarterectomy. In an analysis of postoperative outcomes in the Vascular Quality Initiative registry, Blacks were more likely to be operated on by low volume surgeons or in low volume centers, and when volume is adjusted for, no difference was demonstrated in postoperative stroke/death.<sup>44</sup>

## Peripheral Arterial Disease

The prevalence of PAD in the United States (defined by ankle-brachial index <0.9) is highest among Blacks (7.2%), followed by Whites (3.6%), Hispanics (2.4%), and Asians (2%).<sup>33</sup> There are more than 3.5 million people living in the United States with diagnoses of diabetes and PAD, and the diagnosis of PAD among diabetics has grown at a more rapid rate for Blacks than for Whites.<sup>45</sup> Approximately 2.5% of these patients undergo a vascular procedure each year. More White patients with claudication are treated with endovascular intervention compared with Blacks and Hispanics.<sup>46</sup> Studies have demonstrated that, although 30-day mortality and complication rates are similar among Blacks, Whites, and Hispanics, a higher rate of early graft failure has been demonstrated among Blacks and Hispanics.<sup>46–48</sup> Primary assisted patency and secondary patency are markedly inferior in Black patients, suggesting a more aggressive process of neointimal hyperplasia leading to elevated rates of graft occlusion in the first postoperative year.<sup>47</sup> Biology has been postulated as a contributor to these poor outcomes, but no reliable histologic or genetic data exist to support this hypothesis.

Blacks and Hispanic Americans with PAD have a disproportionately high rate of 2 to 4 times higher nontraumatic lower extremity amputations, compared with Whites (Fig. 17.10).<sup>33,49</sup> The incidence of lower extremity amputations is consistently reported as being higher in racial/ethnic



**Figure 17.10** Racial Trends in Age-Adjusted Hospital Discharge Rates for Nontraumatic Lower Extremity Amputation per 1000 Diabetic Population in the United States, 1990 to 2009.

minority populations even when controlled for atherosclerotic risk factors, severity of PAD, rate of infection, and income.<sup>50–52</sup> Because the decision to amputate is based in large part on the stage of disease at presentation, disparities in disease awareness, medical management, and access to tertiary care and vascular specialists may be key factors affecting these outcomes. Regarding optimal medical management, Black patients with PAD are significantly less likely to have been treated with statins compared with Whites.<sup>47</sup> A smaller proportion of Black patients with diabetes report receiving recommendations on aspirin use from their physicians compared with Whites (61% vs. 76%, respectively).<sup>53</sup> There is also evidence that Blacks are less aggressively treated with lower extremity bypass and endovascular interventions for PAD.<sup>49,50,54</sup> Data from the Nationwide Inpatient Sample of patients admitted for PAD confirm that Blacks and Hispanics are significantly less likely to undergo open vascular bypass or endovascular revascularization than Whites when age, gender, comorbidities, and insurance status are controlled for.<sup>52</sup> Even among patients in the Medicare database, when patient characteristics are controlled for, Black amputees were significantly less likely than Whites to have undergone at least one lower extremity revascularization in the 2 years prior to major amputation.<sup>49</sup> There is no empiric evidence to suggest that Black patients are less inclined to attempt limb salvage prior to proceeding with amputation; rather, differences in presentation or physician decision-making may explain these findings.<sup>49</sup>

Census data have consistently demonstrated higher levels of poverty and lower rates of insurance in Black and Hispanic communities. Patients with less coverage face higher out-of-pocket costs for surgery and therefore may be less likely to opt for intervention. Minorities are often treated

in safety net hospitals, where providers may be overworked and less able to provide adequate treatment for patients with severe disease.<sup>54</sup> The role of hospital and physician volume has not been well explored, but data from the National Surgical Quality Improvement Program demonstrate that relatively more procedures performed in Black patients involved resident trainees compared with procedures performed among White and Hispanic patients. This factor has previously been identified as a contributor to complication rates due to prolonged operative times.<sup>48</sup> Underinsurance may also lead to disparities in access to follow-up care after vascular intervention, including use of antiplatelet and lipid-lowering therapy postoperatively and surveillance duplex imaging.

## Aortic Aneurysm

Population studies have shown that the disease burden of aortic aneurysm is greater among Whites than Hispanics and Blacks. However, even when the disease prevalence is controlled for, Black and Hispanic patients are less likely to undergo elective repair of AAA and more likely to present emergently compared with Whites.<sup>55</sup> This disparity may be secondary to lower rates of access to primary care and decreased rates of screening in minority communities. Blacks and Hispanics are also more likely to receive treatment of AAA at low-volume facilities and more likely to be treated by nonvascular surgeons compared with Whites.<sup>56</sup> Numerous studies have demonstrated a higher morbidity and mortality from elective and ruptured endovascular aneurysm repair among Blacks and Hispanics compared with Whites, even when patient and facility factors are controlled for.<sup>55–59</sup>

When examining open repair of thoracic aortic aneurysms, Blacks have a higher perioperative mortality compared with Whites, even when adjusting for hospital volume.<sup>60</sup> Black, Hispanic, and Native American populations are more likely to undergo thoracic endovascular aortic repair compared with Whites, with no racial/ethnic differences in complications or mortality rates.<sup>61,62</sup>

## Hemodialysis Access

Blacks have more than three times the incidence of end-stage renal disease (ESRD) compared with Whites.<sup>63</sup> A genetic basis for this difference has been identified. An increased risk for progression of chronic kidney disease (CKD) is seen among patients with high-risk variants of the gene encoding apolipoprotein L1 (*APOL1*), which appear at a high allele frequency in populations of West African ancestry.<sup>63</sup> Response to hypertension treatment does not differ by *APOL1* variant group. The risk of CKD progression among Blacks even in the low-risk *APOL1* variant group is higher than in Whites, suggesting that genetic factors alone do not explain these racial disparities.<sup>64</sup> Limited access to specialist care and lack of medical insurance may explain why Black and Hispanic patients with CKD are less likely to receive nephrology care prior to progression to ESRD compared with Whites. As a result, White patients have

a 22% greater chance than Black patients and 32% greater chance than Hispanic patients of initiating hemodialysis with an arteriovenous fistula.<sup>65</sup>

## Addressing Disparities

Addressing racial and ethnic disparities in the prevalence, delivery, and outcomes of care of vascular patients in the United States requires a multilevel approach. At the systems level, the Institute of Medicine has identified the operation of healthcare systems and the legal and regulatory climate in which they operate as a primary source of disparities in care. Federal, state, and institutional policies should be directed at changing the culture within healthcare facilities.<sup>66</sup> Addressing these disparities in access to healthcare at the policy level has been shown to reduce racial and ethnic disparities in outcome. In 2006, Massachusetts expanded healthcare coverage to include 98% of residents and noted significant reductions in racial disparities in vascular disease. Prior to healthcare expansion in that state, non-White patients were 12% more likely to present with severe PAD, 7% less likely to receive revascularization, and 9% more likely to receive an amputation compared with Whites. After the insurance expansion to all Massachusetts residents, these measured disparities by patient race were no longer statistically significant.<sup>67</sup>

At the provider level, bias and uncertainty in clinical communication and decision-making have been identified by the Institute of Medicine as major sources of disparities. Healthcare providers must continue to develop cultural competency to improve clinical communication and therefore the provision of healthcare in cross-cultural situations. Cognitive shortcuts subconsciously introduce bias into medical decision-making. These rapid assessments of patients allow our minds to process complex environmental information in a short period of time by relying on preconceived notions of how a patient is expected to behave. However, they may be detrimental to the choice of the paradigm of care and ultimately affect the medical outcome of the patient.<sup>68</sup> The adherence to evidence-based guidelines allows physicians to rely on logical cognitive processes rapidly, thus reducing reliance on cognitive shortcuts to manage time pressures in the delivery of care. This may be particularly helpful for primary care providers to improve the use of antiplatelet and statin medications for risk reduction in patients with vascular disease. Much like how electronic clinical reminders have been shown to increase detection of AAA,<sup>68</sup> there is excellent evidence to support the use of tracking/reminder systems aimed at providers of racial/ethnic minority patients.<sup>69</sup> Protocols to alert providers to consider referral to a vascular specialist for specific diagnoses can help to address disparities in referral for timely vascular care among racial/ethnic groups.

Patient-level interventions include educational programs to improve patient awareness of interacting with and engaging the healthcare system.<sup>66</sup> Studies suggest that minority patients may be less communicative when the encounter is race discordant and more likely to report medical complaints with race-concordant providers.<sup>70</sup> This may contribute to decreased rates of intervention for claudication and rest pain if these symptoms

are underreported by patients. Efforts have recently been made to increase the presence of minorities in the health profession to facilitate members of minority communities to take advantage of treatment options.<sup>54</sup> Improving patients' knowledge of specialty services offered at high-volume centers particularly for aggressive limb salvage may be helpful to reduce outcome disparities if combined with efforts to improve the ability of patients to take advantage of these opportunities.

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# Noninvasive Vascular Laboratory Quality Assurance and Accreditation

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## INTRODUCTION

The cost of medical care is far greater in the United States of America than in similar developed nations,<sup>1</sup> while other data indicate the health outcomes in the United States lag.<sup>2</sup> These observations have shifted the focus of health policy to health outcomes or value, and have prompted an ongoing effort by funders of healthcare services to convert from volume-based payment to value-based payment.<sup>3</sup> Despite the forces behind this redirection, defining meaningful value and quality in healthcare remains a challenging task. At the most basic level, Rose and Johnson have suggested that Value (V) can be thought of as a quotient of Quality (Q) and Resource utilization (R).<sup>4,5</sup> From a healthcare organization standpoint, these authors believe it is important to increase Q and reduce R as much as possible to extract the most value. This definition roughly equates outcomes with quality and thus healthcare value increases directly with improved outcomes and greater quality.

Medical errors are disturbingly common and dramatically decrease the quality of medical services.<sup>6,7</sup> Medical errors have been reported to be the third leading cause of mortality in the United States, behind heart disease and cancer.<sup>8</sup> Errors

in diagnosis which often involve issues with diagnostic testing are major contributors to medical error and poor patient outcomes.<sup>9,10</sup> The Institute of Medicine (IOM) has proposed six domains that contribute equally to quality care and provide a framework for the evaluation of quality in the vascular lab. These domains are safety, effectiveness, efficiency, timeliness, patient-centeredness and equitable distribution of care<sup>11</sup> (Fig. 18.1). As we consider quality and accreditation in noninvasive vascular laboratory, it is important to note that patient outcomes are multifactorial and that the vascular laboratory is only one factor among many contributing to quality healthcare.

In response to variations in the quality of medical care, Congress passed the Medicare Access and Chip Reauthorization Act of 2015 (MACRA), which authorized the Centers for Medicare & Medicaid Services (CMS) to develop quality and value-based reimbursement models, including the Physician Quality Reporting Program (PQRS), the Value-Based Payment Modifier (VM) and Medicare Electronic Health Records (HER) incentive programs.<sup>12</sup> This act required physicians and healthcare organizations to choose between the Merit-Based Incentive Payment System (MIPS) and the Alternative Payment Model (APM).<sup>13</sup> The overall objective of these programs



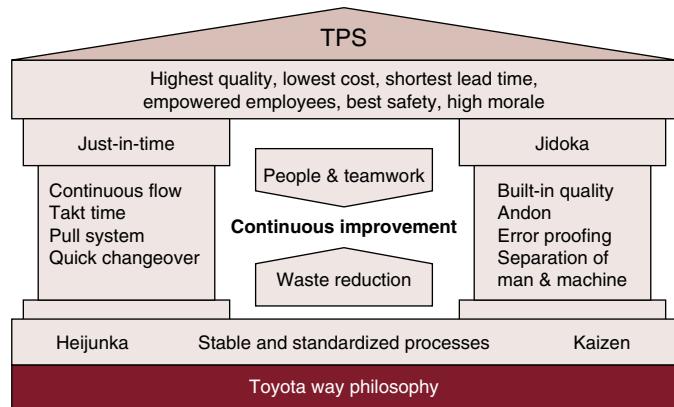
**Figure 18.1** Six Domains of Healthcare Quality. (From <http://www.kp-hc.org/QMI.html>)

was to incentivize healthcare systems and physicians to improve quality of care, reduce healthcare costs and advance healthcare information. These goals are directly in line with the formula mentioned above put forth by Rose and Johnson<sup>5</sup> (see Ch. 200, Alternative Payment Models in Vascular Surgery).

Herein, we describe the evolution of concepts of quality management, the application of these processes to healthcare in general, and the specific implications of these processes for the assurance of quality in the noninvasive vascular laboratory. We discuss the particular challenges of quality measurement in this setting and the adaptations and available mechanisms to institute meaningful and effective quality programs and ultimately achieve consistent quality in the noninvasive vascular laboratory (NIVL). In this regard, we review the potential role of facility accreditation by third parties as a method to manage quality performance and consider the elements of an effective quality program incorporating both internal and external components.

## DEVELOPMENT OF QUALITY PROGRAMS IN MANUFACTURING

Even though a systematic approach to quality improvement is a relatively recent change in healthcare, these strategies have been prevalent in manufacturing for quite some time.<sup>14</sup> The Toyota Production System (TPS) is an integrated socio-technical system developed by the Toyota Motor Corporation between 1948 and 1975 to organize manufacturing and logistics in order to minimize cost and waste and deliver product to the customer in the quickest way possible.<sup>15</sup> This system was based on two pillar concepts: “jidoka,” which means automation with a human touch, and “Just-in-Time” (Fig. 18.2). *Jidoka* refers to the prevention of product defects



**Figure 18.2** Two Pillar System of the Toyota Production System (TPS).

by engaging workers in the quality process and empowering them to identify and act on potential production issues. *Just-in-Time* refers to the concept in which each process in the manufacturing line produces only what is necessary for the next process to continue without interruption. *Just-in-Time* has had pervasive impacts on industrial supply-chain management worldwide, but *jidoka* has greater relevance to healthcare quality. *Kaizen* is the Japanese business philosophy that means continuous improvement or change for the better. The widely employed Lean management model was developed based on TPS and *Kaizen* concepts.

Six Sigma, developed by Motorola Corporation in 1986, is another model of improving efficiency with a focus on process outputs and reduction of defects and variability. The components of Six Sigma are encapsulated by the acronym DMAIC, which refers to define, measure, analyze, improve and control.<sup>16</sup> The philosophies of Lean and Six Sigma are complementary and have been combined and synergized into a more comprehensive quality model referred to as Lean Six Sigma (LSS). The LSS approach has been applied to healthcare since the mid-1990s. Healthcare systems have invested millions of dollars in this model and in similar ones to enhance efficiency, quality and outcomes. However, the positive results of these industrial quality management systems have not been clearly replicated in the medical field.<sup>17</sup> In the LSS model, inefficiencies and breaks in quality are identified, passed up the chain to directors and leaders, and then changes are passed back down to middle managers for implementation. The pure TPS model rejects the top down model of quality management and attempts to create a culture of continuous improvement from the assembly line worker up to the chief executive officer. All are empowered to adapt their work in real time to improve the organization’s product and service, and thus all members of the organization are invested in its improvement.

## Components of Quality Programs

Classically, quality systems are composed of two major components: quality control (QC) and quality assurance (QA).<sup>18</sup> QC focuses on fulfilling specific quality requirements and grew from the need for manufacturing processes to consistently

meet engineering specifications. QA is the overarching component of a quality system that encompasses QC activities and focuses on providing confidence that quality requirements are fulfilled. QA lends confidence both internally to management and externally to customers, governing agencies and certifiers. For QC to be understood in the NIVL, the vascular laboratory output (diagnostic studies) must be viewed as products that must conform to certain quality requirements or standards to meet the needs of the consumers (clinicians) and customers (patients).

Inspection and auditing are important processes in QC and QA, respectively. Inspection is the exercise of measuring, testing and comparing characteristics of a product to specific requirements, and thus the determination of conformity to a set standard. Auditing is an activity used to compare actual conditions with requirements and to report the findings to management. The distinction between these processes is important. An audit can utilize inspection techniques but should not be involved in verification that results in acceptance or rejection of a service. An audit evaluates the process and controls for production and verification.<sup>19</sup> Through these processes, both QA and QC are designed to maintain standards in production and quality.

Modern quality programs in healthcare are referred to as either total quality management (TQM) or continuous quality improvement (CQI). These are structured organizational processes for involving personnel in planning and executing continuous improvements to provide quality healthcare that meets or exceeds expectations.<sup>20</sup> This is very similar to the Toyota Motor Corporation culture of continuous improvement at all levels of the organization. There are several key characteristics that are common to TQM and CQI. These include: a link to key elements of the organization's strategic plan; a quality council that includes top leadership at the institution; training programs for personnel; mechanisms for selecting improvement opportunities; formation of process improvement teams; staff support for process improvement; and personnel policies that encourage participation in process improvement at all levels.<sup>15</sup> Although some of the components of a TQM/CQI program are designed more for large-scale healthcare organizations (hospital, medical system, large private practice), the principles are just as applicable to smaller in-hospital or free-standing diagnostic units. At its base, CQI recognizes that customer requirements are the key to customer quality and that customer requirements change over time. Improvements in technology, education, information management, and the economy all contribute to the need for continuous quality improvement.<sup>15</sup>

An essential component of any effective TQM/CQI program is the avoidance of personal blame and a focus on managerial and professional processes needed to obtain specified outcomes. Successful continuous improvement, *kaizen*, relies on engagement, empowerment and commitment of personnel at all levels to quality goals. In healthcare, this philosophy has been incorporated into the concept of Just Culture<sup>21</sup> and the more expansive Culture of Safety.<sup>22</sup> These notions are particularly relevant in a NIVL where there is often a hierarchical

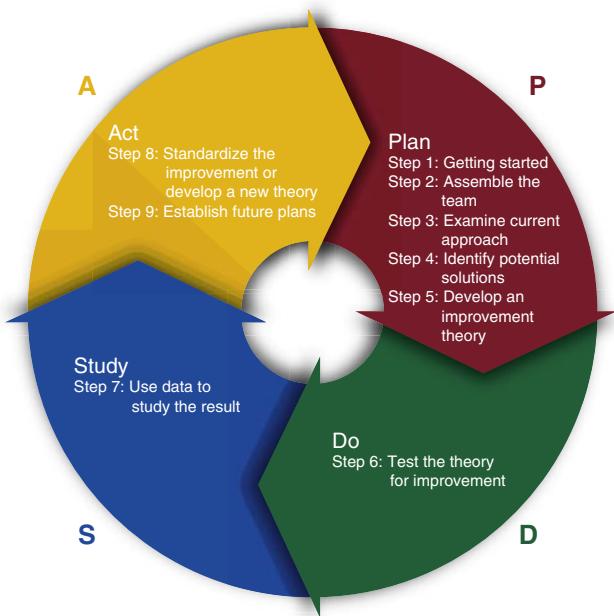
structure with a medical director, laboratory supervisor, lead technician and multiple vascular technologists and the daily workflow typically separates the technical activities of sonographers and the interpretive functions of medical staff. By engaging all personnel in the NIVL as stakeholders in the quality improvement process, quality becomes more than just an abstract idea, but rather a source of pride with resultant improved performance and morale.

The application of TQM/CQI to healthcare endeavors requires adaptations to several specific conditions not found in other industries. In healthcare, the consumer (clinician), the customer (beneficiary, patient) and the payer (government/insurer) are separate with parallel but not identical goals. There is a lack of transparency regarding costs and benefits and a significant knowledge disparity among the parties. Furthermore, the uncertainties related to variability of human biology, the complex interactions of pathology and the limits of available clinical data make the identification and validation of uniform quality metrics vexing. In addition, much of the relevant data itself is subject to patient-related privacy protections (Protected Health Information [PHI] under HIPAA regulations) and peer review regulations at state and federal levels. Several compliant information gathering approaches have been developed to document current practices and identify pathways for improvement, including Quality Improvement Organizations (QIO) and Patient Safety Organizations (PSO), among others.<sup>23,24</sup> Beyond these considerations, in the assessment of overall patient outcomes and thus the quality of the healthcare system, it is difficult to determine the contribution of the diagnostic process in general and more so of the performance of a particular diagnostic facility or study.

## FUNDAMENTALS OF TOTAL QUALITY MANAGEMENT

In 1931, Walter Shewhart first published on the control chart and the Plan, Do, Check, Act (PDCA) cycle, often called the Shewhart cycle.<sup>25</sup> The cycle involves the following steps: (1) **Plan** – identify which changes are most desirable and develop a plan to reach the objective; (2) **Do** – search for data on hand to answer the question at hand and carry out a change or test; (3) **Check** – observe the effects of the change or test; and (4) **Act** – review the results and set a process of change into practice or modify the plan and repeat the cycle<sup>15,16</sup> (Fig. 18.3).

A variant of the PDCA cycle often used in healthcare is called the FOCUS-PDCA model, and was developed by the Hospital Corporation of America (HCA).<sup>26</sup> FOCUS is a lead-in to the PDCA cycle and stands for: (1) Find a process to improve; (2) Organize an improvement team; (3) Clarify understanding on the process; (4) Understand why there is process variation; and (5) Select the process improvement.<sup>7</sup> The FOCUS lead-in to the PDCA cycle lays the groundwork for the Plan phase of the PDCA cycle. After completion of the cycle and once a goal has been achieved, other areas needing quality improvement can be identified and tackled.



**Figure 18.3** Plan, Do, Check (Study), Act Cycle. (From: Tribal Evaluation Institute Continuous Quality Improvement. <http://www.tribaleval.org/cqi/plan-do-study-act-pdsa/>)

## QUANTITATIVE IMAGING BIOMARKERS

Biomarkers are characteristics that are objectively measured and are evaluated as indicators of normal biologic function, pathologic processes or response to a therapy.<sup>27</sup> Imaging technologies provide information on anatomy, physiology and function; therefore, they may be considered biomarker measurement processes. When quantifiable information is gathered from medical imaging pertaining to either normal findings or severity of disease, the procedure is considered quantitative imaging and the data generated are quantitative imaging biomarkers (QIB).<sup>28</sup>

There is certain terminology important for the understanding of QIB and measurements. A **Measurand** is the quantity intended to be measured. A **Reference value** is a generally accepted value with a small amount of uncertainty used as a basis for comparison with values of quantities of the same kind. **Precision** is the closeness of agreement between the measurand values obtained by replication using the same or similar experimental units under specified conditions. **Repeatability** refers to the measurement precision with conditions that remain unchanged between replicate measurements. **Reproducibility** is the measurement precision with conditions that vary between replicate measurements. **Bias** is an estimate of the systemic measurement error. **Truth or true values** are the real or actual values of a quantity to be measured.<sup>23,24</sup>

In healthcare, truth and true values are often nebulous and possibly more idealistic than absolutes. All measurement has error and uncertainty, so unequivocal truth is only a theoretical construct. The term **gold standard** is used often in healthcare to indicate a reference standard for medical imaging. This term

		True class		Measures
		Positive	Negative	
Predicted class	Positive	True positive <i>TP</i>	False positive <i>FP</i>	Positive predictive value (PPV) $\frac{TP}{TP+FP}$
	Negative	False negative <i>FN</i>	True negative <i>TN</i>	Negative predictive value (NPV) $\frac{TN}{FN+TN}$
Measures		Sensitivity $\frac{TP}{TP+FN}$	Specificity $\frac{TN}{FP+TN}$	Accuracy $\frac{TP+TN}{TP+FP+FN+TN}$

**Figure 18.4** Contingency Matrix and Measures Calculated Based on a 2 × 2 Contingency.

assumes that a measurement obtained by a specific modality, the gold standard, is the true value and has no error.

**Accuracy** is a term that reflects both bias and precision but there is no consensus on how to combine these two ideas.<sup>29</sup> Accuracy is generally assessed by comparison to a gold standard. If accuracy is used to infer the quality of a measurement, then there should be a complete description of the uncertainty within these comparisons, including bias and precision in the gold standard itself. Accuracy assessment by comparison to a gold standard necessitates the existence of a relevant gold standard and repeated measurements of the measurand using the two modalities in question. Utilization of a gold standard comparator to assess the accuracy of vascular noninvasive tests can be difficult as some comparator modalities provide anatomic information and others physiologic information. In some cases (venous testing for deep venous thrombosis) vascular testing is itself the gold standard. If comparison to a gold standard is not possible, then blinded repeat examination by other laboratory personnel, such as alternative sonographers and interpreting physicians, could be employed. This methodology, which is in essence assessment of precision, lends itself to limitations in terms of operator and interpreter bias.

If a gold standard test exists, there are certain parameters that can be used to describe concordance between this standard and the laboratory test in question. **Sensitivity** is the likelihood that the NIVL test will be positive when the gold standard indicates the disease is present. **Specificity** is the likelihood that the NIVL test will be negative when the gold standard indicates the disease is absent. **Positive predictive value (PPV)** is the proportion of NIVL tests with a positive result that are correct; that is, the disease is present by the gold standard. **Negative predictive value (NPV)** is the proportion of NIVL tests with a negative result that is correct; that is, disease is not present by the gold standard.<sup>30</sup> These basic parameters can be calculated from the 2 × 2 binary contingency table illustrated in Figure 18.4. The actual PPV and NPV of a test in clinical practice depends significantly

on the prevalence of the condition to be tested in the population under study (pretest probability).

In this regard, it is important to not lose sight of the other domains of quality care. The effectiveness of a diagnostic study goes beyond these simple calculations and is based on the test's utility in clinical decision-making. There is often wide variation in the use of diagnostic tests based on their perceived benefit in the evaluation of specific disease processes and on their contribution to the overall care of the patient. Scholarly societies and expert panels have developed consensus guidelines in the form of appropriate use criteria documents for various tests and disease states.<sup>31–33</sup> However, it is difficult to determine the overall utility of a vascular laboratory study and its relationship to the ultimate clinical outcome even when evaluated under the appropriateness of use criteria. Other commonly employed measures of test or lab effectiveness include patient and provider perceptions of the test's role in care. Surveys are often performed in NIVL to evaluate these aspects of patient-centered care. There is also an interest among patients, providers and payers to increase the overall efficiency of diagnostic tests as judged by a reduced need for either repeat testing (same modality) or supplementary or confirmatory testing with other modalities.<sup>7</sup>

## ACCREDITATION

The purpose of any accreditation program is to provide assurance and external validation that an organization or facility is adhering to recognized standards and quality. An accreditation process reviews technical competence of the staff, quality assurance of test data, records and documentation, validity of testing methods and calibration and maintenance of testing equipment. There are three main reasons why healthcare organizations consider accreditation to support CQI processes. These include: compliance with regulatory requirements, competitive advantage in the marketplace, and a desire for actual impartial guidance and objective assessment of process improvement, thereby enhancing the organization's efficiency and effectiveness.

Quality management and assurance can be a time-consuming and complex process that requires significant resources of personnel, time and budget. Hospital systems, large medical centers and large independent providers have the ability to devote substantial resources to in-house quality processes following the general principles and practices noted earlier. However, much of these efforts is directed at specific systemic quality concerns and compliance with regulators or achievement of third-party recognition. Hospital accreditation by the Joint Commission, DNV GL Healthcare (Det Norske Veritas/Germanischer Lloyd), or other organizations, or recognition by organizations such as Leapfrog, Magnet, etc., have significant impacts, but these programs do little to directly evaluate quality in diagnostic imaging.<sup>34–36</sup> Smaller independent organizations or labs often lack the resources to conduct meaningful CQI activities independently.

### Benefits of Accreditation

Since QA and CQI can be so resource intensive, both in diagnostic units within large organizations and in free-standing facilities,

formal accreditation programs by third party organizations can provide a framework, a set of tools and guidance for diagnostic facilities to establish and deploy quality systems relevant to their actual work. There are four organizations that are approved by the Centers for Medicare & Medicaid Services to accredit various medical facilities including diagnostic imaging units: the American College of Radiology (ACR), the Joint Commission, RadSite, and the Intersocietal Accreditation Commission (IAC).<sup>37</sup> Professional organizations including the American Institute for Ultrasound in Medicine (AIUM) and the American College of Cardiology (ACC) also provide accreditation services for certain imaging facilities.<sup>38–41</sup> The structure, scope, focus and rigor of imaging accreditation programs are influenced by the history and philosophy of the accrediting body. Some programs are quite broad and general, others are specialty specific. The IAC grew from the Intersocietal Commission for the Accreditation of Vascular Laboratories (ICAVL), which was founded in 1990 with a unitary focus on quality in vascular ultrasound and foundational support of the Society for Vascular Surgery. The IAC program adopted and has maintained an intersocietal approach in clear recognition that vascular noninvasive testing is a multispecialty modality and that the public good would be best served through a collaborative process of both standard setting and performance evaluation.

Accreditation programs begin with the setting of performance standards for each component of the diagnostic unit's activities, the physical plant, equipment, policies, procedures, personnel, safety, maintenance and efficiency. Standards may be set by guidelines of specific societies or professional organizations, or through collaborative consensus using the best available recommendations in the literature and the judgment of subject matter experts. Compliance to standards is required for accreditation and is assessed on a periodic basis through submission of data and site visits. The stringency of these review and audit functions varies among accreditation organizations. For example, only the IAC-VT accreditation program requires submission of complete diagnostic cases with all images for expert review based on tested, validated criteria related to indications, technical quality, interpretive accuracy and consistency, and lab efficiency.

For a diagnostic imaging accreditation program to actually improve quality broadly the program must balance the ideal and the practical. Standards must be data-driven, reasonable and achievable, not just in highly resourced major medical centers, but throughout the medical community. Standards must evolve as medical knowledge and technology advance. Standards cannot be perceived as self-serving, exclusionary or favoring one particular practice group. Monitoring of compliance cannot be excessively costly or burdensome and should be focused on daily routine performance as much as possible. A collaborative relationship between the facility and the accreditor should be the best approach and technological advances in information technology and image sharing may allow the development of such models soon.

### Shortcomings of Current Accreditation Models

The benefits of accreditation of the NIVL to patients and health-care systems are clear. The limitations of the current models of accreditation may be less obvious and deserve consideration.

**BOX 18.1****Intersocietal Accreditation Commission Vascular Testing (IAC-VT) QI Standards<sup>44</sup>****Standard – QI Program**

- 1.1C The facility must have a written Quality Improvement (QI) program to evaluate all types of procedures performed in the facility on an ongoing basis. The QI program must include the QI measures outlined below but may not be limited to the evaluation and review of:
- 1.1.1C test appropriateness
  - 1.1.2C technical quality and, if applicable, safety of the imaging
  - 1.1.3C interpretive quality review
  - 1.1.4C report completeness and timeliness
  - 1.1.5C case review.

**Standard – QI Oversight**

- 1.2C The Medical Director, staff and/or an appointed QI Committee must provide oversight to the QI program including but not limited

to review of the reports of QI evaluations and any corrective actions taken to address any deficiencies.

**Standard – General QI Measures**

- 2.1C Facilities are required to have a process in place to evaluate the QI measures outlined in sections 2.1.1C through 2.1.5C.

**Standard – QI Meetings****3.1C Quality Improvement (QI) Meetings**

- 3.1.1C The facility must have a minimum of two QI meetings per year, one of which is to review the results of the QI analyses and any additional QI-related topics.
- 3.1.2C All staff must participate in at least one meeting per year.

From: Intersocietal Accreditation Commission. IAC Standards and Guidelines for Vascular Testing Accreditation. Available at: <https://www.intersocietal.org/vascular/standards/IACVascularTestingStandards2020.pdf>.

Most accreditation programs require a comprehensive and rigorous assessment of all of the components underlying a facility's performance, including physical plant, equipment, personnel, policies (procedural protocols, interpretive), documentation and efficiency. Facilities must assemble large quantities of supporting documents and other materials to achieve initial accreditation and resubmit similar information for reaccreditation on a typical 2–3 year accreditation cycle. This can present a substantial burden to lab staff and is a real barrier to greater engagement in accreditation as pathway to improve lab quality for many facilities.

The cyclical nature of accreditation with a focus on periodic comprehensive evaluation shifts attention from day-to-day quality within the lab and fails to capture changes that can significantly degrade lab quality on a shorter time scale. Examples include changes in personnel, protocols, leadership, interpreting staff, administration or equipment, which can lead to both subtle and major changes in lab consistency and overall performance. Many accreditation programs for imaging units do not require submission of actual work product (case studies with protocols, images, interpretations, reports) on initial or reaccreditation. The IAC-VT program requires case submission, but only a small sample of "best work" as judged by the facility. Although review of actual case material is a very sensitive index of lab performance, the small sample size, the potentially biased case selection and the infrequent nature of review undermine the effectiveness of this process for CQI.

To address these issues, some accreditation models recommended periodic in-house peer review through quality improvement and quality assurance meetings. There has been little specific guidance on the conduct of such exercises. In the vascular lab, the traditional QA activity has been correlative comparison of vascular noninvasive tests with alternative imaging modalities or surgical or pathological findings. While these comparative analyses of specific cases have substantial educational value and provide some external validation of lab findings, they often divert attention from review of day-to-day

operational processes and performance. Although there is considerable benefit to continuous evaluation of all studies performed in a NIVL and this kind of review is the cornerstone of all CQI, this approach has prohibitive cost in terms of time and resources. Even though accreditation is an accepted standard for NIVL quality, there is a lack of literature discussing how effective obtaining this accreditation is on actual quality in noninvasive cardiovascular imaging.<sup>42,43</sup>

## **PROSPECTS FOR IMPROVED MODELS OF ACCREDITATION**

Accreditation models are evolving with our concepts of CQI in healthcare and in response to regulatory and market demands. Advances in information technology have facilitated this evolution.

We consider the changes in the quality process of one accreditation model as an illustration of the current state and future potential. In 2020, IAC-VT released an updated revision of its quality standards for vascular labs (**Boxes 18.1 and 18.2**).<sup>44</sup> The thrust of this revision was to redirect the focus of quality from intermittent external review to a more frequent internal CQI process. The new standards retain but de-emphasize traditional case correlation analysis and mandate internal review and evaluation of the entire lab process from receipt of an imaging request through to issuance of a finalized interpretative report. The internal review was focused on four essential areas of performance: appropriate use, imaging quality, interpretive quality and report completeness and timeliness. In order to facilitate these review activities, IAC developed an online QA application and identified a small set of specific metrics for review by the facility. This set of metrics was selected from the comprehensive validated metrics used by expert reviewers when evaluating cases submitted for review at accreditation or reaccreditation. Several of these metrics were chosen because they have been problem areas for many labs at reaccreditation. The online nature of the tool creates the

**BOX 18.2****Intersocietal Accreditation Commission Vascular Testing (IAC-VT) QI Standards – Specific QI Metrics<sup>44</sup>****Standard – General QI Measures**

2.1C Facilities are required to have a process in place to evaluate the QI measures outlined in sections 2.1.1C through 2.1.5C.

## 2.1.1C Test Appropriateness

2.1.1.1C The facility must evaluate the appropriateness of the test performed and categorize as:

- i. appropriate/usually appropriate
- ii. may be appropriate
- iii. rarely appropriate/usually not appropriate.

## 2.1.2C Technical Quality Review

2.1.2.1C The facility must evaluate the technical quality and, if applicable, the safety of the test performed. The review must include but is not limited to the evaluation of:

- i. the images/procedure data for suboptimal images/procedure data or artifact
- ii. completeness of the study

iii. adherence to the facility imaging/data acquisition protocols.

## 2.1.3C Interpretive Quality Review

2.1.3.1C The facility must evaluate the quality and accuracy of the interpretation based on the acquired images/procedure data for all types of procedures performed in the facility.

## 2.1.4C Final Report Completeness and Timeliness

2.1.4.1C The facility must evaluate the final report for completeness and timeliness as required in the Standards.

## 2.1.5C Case Review

2.1.5.1C Case review with any appropriate imaging modality, surgical findings, clinical outcome or other comparison of a minimum of four cases annually with at least two cases per relevant testing area (extracranial, intracranial, arterial, venous, visceral, screening).

From: Intersocietal Accreditation Commission. IAC Standards and Guidelines for Vascular Testing Accreditation. Available at: <https://www.intersocietal.org/vascular/standards/IACVascularTestingStandards2020.pdf>.

potential for IAC to perform an in-house review of the labs' self-evaluations, to provide the labs with benchmarking against similar facilities and to provide more continuous guidance to support in-lab programs. If accepted, this method of online case review could facilitate or supplement complete case submissions at reaccreditation, simultaneously reducing the burden on labs and giving a more realistic assessment of daily lab performance.

Traditional clinical correlation case reviews remain an important part of the CQI process under the new IAC-VT standards. Case review can take various forms as part of twice yearly QA meetings and be a vital continuing education activity for lab personnel as well as an opportunity to engage the technologists, interpreting physicians and support staff in a sense of *kaizen* in which everyone has a role in the facility's quality and overall success.

## CONCLUSION

Quality improvement and quality assurance are of paramount importance in any service industry. It is essential to understand that the noninvasive vascular laboratory provides a service and product to a broad set of consumers. In order to deliver appropriate, high-quality healthcare, vascular laboratory testing must be of the highest caliber. This can be accomplished through implementation of effective quality assurance and quality improvement programs. Achieving consistent quality can be a difficult task that demands significant resources which may not be available in all settings. Third party accreditation bodies can be valuable partners in this quest for quality, but the accreditation programs must be relevant and meet the specific needs of the vascular lab. Although accreditation can help confirm or refute the quality of the laboratory imaging at the time of accreditation, CQI requires the active participation of everyone in the NIVL.

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# Clinical Evaluation of the Arterial System

PHILIP P. GOODNEY

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This chapter focuses on the role of patient history and physical examination in evaluating the various disease states secondary to arterial pathology. In general, the lower extremities provide a model for the clinical evaluation of patients with vascular disease and can be used to demonstrate the value of an organized approach to the history and physical examination of the patient.

## OVERVIEW OF THE CLINICAL EVALUATION

The patient’s chief complaint should be determined; the physical examination should be correlated with the history and should provide a bridge to the pathophysiology of the disease process.<sup>1,2</sup> As an example, aortoiliac obstructive disease will

often be associated with more proximal symptoms of claudication involving the buttock, hip, or thigh. If the clinical history is accurate, the examiner should expect that the femoral pulse will be absent or decreased. If it is not, the history and assumptions regarding pathophysiology should be questioned.<sup>3-5</sup>

When the history and physical examination are completed, diagnostic studies can be ordered, if necessary, to further localize the disease or quantify the extent of the process. Therapy is ultimately driven by the natural history of the disease process and its impact on quality of life, as well as by the patient’s risk factors and functional status. A relatively benign natural history or significant and unmodified patient risk factors may indicate an initial course of medical management, risk factor modification, and observation, whereas a threat of tissue loss may indicate the need for a more aggressive intervention.

## Clinical History

Typically, the symptoms of arterial disease can be broadly classified into the following categories: pain; weakness; neuromsensory complaints, including warmth, coolness, numbness, and hypersensitivity; discoloration; tissue loss and ulceration. Critical elements include the initial onset of symptoms (acute or chronic); progression or changes since the initial onset; location (unilateral, bilateral, proximal, distal); character or quality of the symptom or complaint; some measure of the extent of disability or limitation; the context or factors precipitating or aggravating the symptoms (activity, position, temperature, menses, vibration, pressure); factors mitigating or relieving symptoms; and associated signs, symptoms, or risk factors. In the assessment of vascular disease, the history is important. As will be seen, variations from the expected history or pattern of findings may suggest additional disease processes that might be included in the differential diagnosis.

## Physical Examination

The physical examination links the clinical history and the pathophysiology of the arterial disease process. The pathology associated with arterial disease can be broadly classified into inflammation-mediated arterial wall changes, arterial wall irregularity or ulceration, stenosis/occlusion, and dilation and aneurysmal degeneration, in contrast to the pathophysiology of venous and lymphatic disorders.<sup>6,7</sup>

The physical examination should progress from inspection, to palpation, to auscultation. On inspection, the extremity should be assessed for evidence of skin changes, including atrophy, cyanosis or mottling, pallor, and rubor; hair distribution; and abnormalities in nail growth. The presence and location of edema should be identified and quantified. Tissue loss and ulceration should be noted and fully described, including the location, size, and depth, and the presence of associated cellulitis and inflammation should be documented. Motor function should be documented. On initial palpation, changes in temperature and sensation should be noted and compared with the contralateral extremity. All accessible pulses should be evaluated. At a minimum, pulses should be classified as absent, decreased, or normal. A prominent or widened pulse may suggest aneurysmal degeneration.

## Synthesis of History and Physical Examination

Assessment of a patient with arterial disease is unique in that it is frequently possible to make a diagnosis and predict the underlying anatomic pathology on the basis of history and physical examination alone. This is important because the anatomy of the disease process can often correlate with the location of symptoms. The history and physical examination should be thought of as a system of checks and balances. Symptoms should correlate with the physical examination and suspected pathology.

## The Evolving Role of Telemedicine in the History and Physical Exam for Vascular Disease

As with many aspects of healthcare, technology has changed the landscape in which we practice. Many fields rely heavily on remote interaction between treating physicians and their patients. While many believe that telemedicine in vascular surgery is a new and evolving concept, it has been studied for more than 20 years<sup>8-12</sup> (see Ch. 204, Telemedicine in Vascular Surgery Practice). For example, Endean and colleagues described vascular evaluation by teleconference, remote Doppler assessment, and the use of physician extenders in a manuscript published in 2001.<sup>8,9</sup> The barriers they described at the time sound strikingly familiar to the challenges we all face, and electronic health records today comfort with technology and successful execution of technology-based assessment strategies. While this is an evolving strategy, future advances will undoubtedly change the way we perform physical examination in the future.

For many healthcare providers, changes incurred by the coronavirus pandemic in 2020 spurred on a rapid adoption of telemedicine. Billing processes were rapidly changed to allow healthcare providers to expand the use of telehealth, and guidelines from the Centers for Disease Control and Prevention encouraged healthcare providers and patients to use telehealth during the pandemic whenever possible. Figure 19.1 shows the locations in the United States where billing legislation allowed implementation of telehealth visits.<sup>13</sup> While many visits with patients with vascular disease could readily transfer to telehealth, such as assessment for abdominal aortic aneurysm using cross-sectional imaging, there are other aspects of history and physical – frailty assessment, pulse exam, and patient counseling – that may fare better using in-person visits. The pandemic undoubtedly accelerated this tool, which will certainly remain in use for years to come.

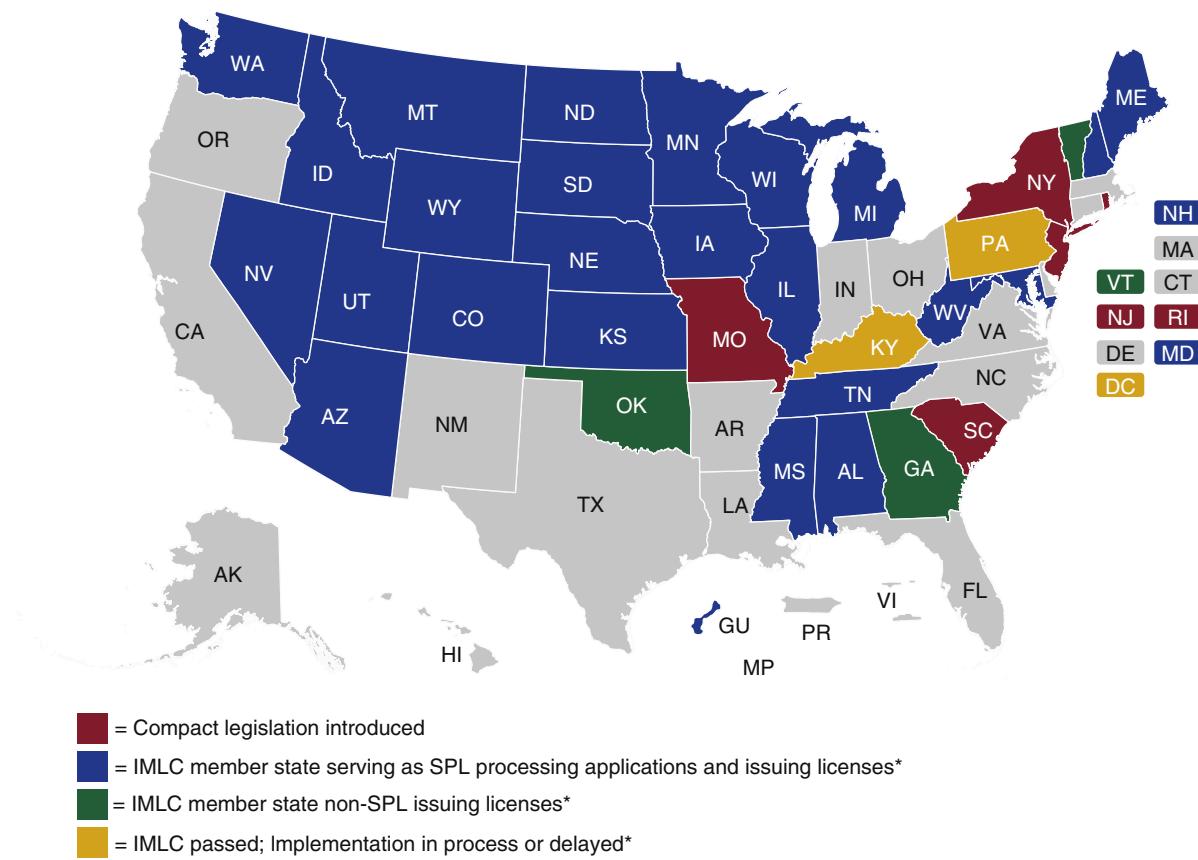
Documentation and billing aspects, as well as technology for pulse assessment, are a rapidly evolving field, and will certainly progress to help keep vulnerable patients at home whenever remote assessment is allowable.

## HISTORY IN PATIENTS WITH ARTERIAL DISEASE

Patients with peripheral arterial disease (PAD) may initially be seen after acute arterial occlusion or with symptoms of chronic arterial insufficiency. Regardless of whether the onset of symptoms is acute or chronic, the chief complaint is generally pain or discomfort. As part of the initial history, it is important to determine the acuteness of onset, the character and intensity of the pain or discomfort, changes in the character and intensity since onset, and its location.

### Acute Arterial Occlusion

Acute arterial occlusion may be either embolic or thrombotic in etiology (see Ch. 103, Acute Limb Ischemia: Evaluation, Decision-Making and Medical Treatment). Classically, acute



**Figure 19.1** Locations where Telehealth Legislation Allows Remote Visits. *IMLC*, Interstate Medical Licensure Compact; *SPL*, State of Principal Licensure.

arterial occlusion is associated with the six Ps: pain, pallor, pulselessness, paresthesias, paralysis, and poikilothermy (meaning changing to room temperature; i.e., a cold extremity). Symptoms can occur within minutes to hours after acute arterial occlusion and are associated with a sudden, dramatic decrease in perfusion. Classically, a patient will complain of generalized pain, severe, and not well localized. The patient will notice a change in the color of the extremity, a decrease in sensation, and coolness to touch. Absent motor function is consistent with severe limb-threatening ischemia.

### Acute Arterial Occlusion of the Lower Extremity

As a rule, patients with acute arterial occlusion secondary to an embolic etiology will not have a history of claudication or symptoms suggestive of chronic occlusive arterial disease. Embolic occlusion of the iliac, femoral, or popliteal arteries is frequently associated with a history of atrial fibrillation, and the patient may have had a previous embolic event. Patients with thrombotic occlusion of the iliac, femoral, or popliteal arteries will frequently have a history of claudication and may have previously undergone arterial bypass or intervention.

### Atheroembolism: “Blue Toes Syndrome”

Atheroembolic debris arising from atherosclerotic plaque or ulcerations in the aorta, as well as the iliac, femoral, and popliteal

arteries, can result in distal small-arterial occlusion (see Ch.106, Atheromatous Embolization and Its Management). Progressive renal insufficiency can be associated with atheroemboli originating in the thoracic or suprarenal aorta. Patients may have undergone some form of catheter-based procedure involving manipulation of a catheter in the aortic arch or the thoracic and abdominal aorta, or the embolism may be spontaneous.

### Acute Arterial Occlusion of the Upper Extremity

While less common, acute arterial occlusion may also occur in the upper extremities. The onset and symptoms are similar to those seen in the lower extremities. Emboli associated with atrial fibrillation or recent myocardial infarction are more common, but may also originate from aneurysmal disease of the arch or upper extremity arteries. Atheroemboli involving the hand or digits may arise from atherosclerotic irregularity and plaque in the aortic arch, or from thrombus associated with a subclavian artery aneurysm.

### Chronic Obstructive Arterial Disease

Patients with PAD most commonly have long-standing symptoms. Chronic PAD can be categorized according to the Rutherford classification system of occlusive arterial disease, which encompasses a spectrum of symptoms, beginning with effort

discomfort (claudication) and progressing to pain at rest and tissue loss. Claudication is derived from the Latin word *claudicare*, which means to limp or be lame. Thus, claudication involves the lower extremities and is associated with walking. Effort-induced discomfort with activity involving the upper extremity can be associated with stenosis or occlusion of the subclavian and axillary arteries. The Rutherford classification system – a clinical staging system – ranges from asymptomatic (stage 0), to mild or moderate claudication (stage 3), to severe (stage 6).<sup>14,15</sup>

### Lower Extremity Claudication

Claudication symptoms are associated with walking, and relief occurs promptly after the cessation of activity. Complete relief of symptoms should occur within 5 to 10 minutes, and it should not be necessary for the patient to sit to obtain relief. Symptoms may be described as cramping, aching, fatigue, or numbness, and the common denominator is an association with exercise or activity.

Symptoms may have been present for months or years. Anatomically, lower extremity PAD is broadly classified as aortoiliac, femoropopliteal, or tibial. Depending on the location of the arterial obstruction, the patient may have pain in any of the three major muscle groups of the lower extremity: the buttock, thigh, or calf. Symptoms may involve one or more of these muscle groups and may progress from the proximal to the distal part of the extremity or from the calf to the thigh with continued activity. Symptoms will often occur in the muscle group immediately distal to the obstruction. Whereas obstruction of the superficial femoral artery will cause calf discomfort, aortoiliac disease will result in symptoms involving the buttock or thigh. However, patients with aortoiliac disease can also have associated or isolated discomfort of the calf because the calf is the most distal large muscle group and is used extensively in walking. The triad of intermittent claudication, impotence, and absent femoral pulses is associated with aortoiliac occlusion and is often referred to as Leriche syndrome. In his initial descriptions of the disease process, Leriche also identified widespread atrophy of the lower extremities and a pale appearance of the extremities and foot.

Some patients with PAD confirmed by noninvasive vascular testing may not complain of claudication because comorbid conditions may limit their exercise tolerance. Conversely, other patients may have classic symptoms of claudication but a normal pulse examination. Because initial assessment generally occurs while the patient is at rest on the examining table, it is important to remember that the claudication occurs with walking. In cases when there is a mismatch between the history and physical examination, the physical examination may need to be repeated after exercise.

### Conditions Mimicking Arterial Claudication

Classically, claudication is associated with arterial stenosis or occlusion; it is induced by exercise and relieved by rest, and has an onset that is consistently reproducible. Inconsistencies in the history should suggest the possibility of other causes of the patient's symptoms. Included in the differential diagnosis

of claudication are musculoskeletal, neurologic, and venous pathologies, the most common of which are osteoarthritis, spinal stenosis, and venous outflow obstruction. Symptoms that occur at rest, occur with standing, or are associated with positional changes may suggest osteoarthritis, spinal stenosis, radiculopathy, or venous claudication (Table 19.1).

Patients with atypical claudication of nonarterial etiology will often note pain with exertion, yet the pain does not stop the individual from walking, may not involve the calves or other major muscle groups in the leg, or does not resolve within 10 minutes of rest. Patients may report the same type of pain in both legs regardless of the associated presence of occlusive disease. Frequently, patients with atypical symptoms often report walking impairment because of joint pain or shortness of breath.

Ultimately, in the evaluation of an individual with leg pain, the examiner has to be cognizant of the patient's comorbid conditions in an effort to offer the most complete treatment. Newman and colleagues compared answers to the Rose Questionnaire in patients with and without arthritis, all of whom had a decreased ankle–brachial index and exertional leg pain.<sup>16</sup> Both groups had pain in the calf or calves on walking at a normal pace, while in a hurry, or when walking uphill. However, the patients with arthritis had a higher incidence of pain when standing still or sitting, were less likely to continue walking after the onset of pain, and required more than 10 minutes to obtain relief after they had stopped walking (Table 19.2).

One important differential diagnostic consideration is neurogenic claudication due to spinal stenosis. This can result from a wide range of conditions causing compression of the spinal cord or its nerve roots in the region of the lumbar spine. It may be associated with aging, arthritis, or inherited deformities of the spine. The symptoms of spinal stenosis are frequently inconsistent in their relationship to exercise or activity.

In addition, venous claudication, due to a proximal venous obstruction resulting in impaired venous outflow, may be confused with claudication of arterial etiology. When an individual begins to exercise or engage in some activity, venous outflow cannot accommodate the increase in arterial flow to the extremity, and high venous pressure develops. The veins become engorged and tense, which causes a bursting sensation or pain that is slowly relieved by rest. The same symptoms can be seen in individuals with chronic venous insufficiency, where persistent venous thrombosis or valvular insufficiency can cause an increase in ambulatory venous pressure that results in chronic lower extremity edema, as well as evidence of postphlebitic skin changes. In these patients, swelling is frequently minimal in the morning but progresses throughout the day with increased activity and dependency of the extremity (see Ch. 20, Clinical Evaluation of the Venous and Lymphatic Systems).

### Other Considerations in Young Patients

Claudication of a vascular etiology most commonly occurs in patients 50 years or older. In younger patients, symptoms of effort discomfort can be associated with popliteal artery obstruction from muscular or tendinous entrapment or

**TABLE 19.1** Differential Diagnosis of Claudication

Condition	Location of Pain or Discomfort	Characteristic Discomfort	Onset Relative to Exercise	Effect of Rest	Effect of Body Position	Other Characteristics
<b>Arterial Conditions</b>						
Intermittent claudication of the calf	Calf muscles	Cramping pain	After same degree of exercise	Quickly relieved	None	Reproducible
Intermittent claudication of the hip, thigh, buttock	Hip, thigh, buttocks	Aching discomfort, weakness	After same degree of exercise	Quickly relieved	None	Reproducible
Popliteal artery entrapment	Calf muscles	Cramping pain	After exercise	Quickly relieved	Aggravated by extension of the foot	Typically seen in younger patients
<b>Venous Conditions</b>						
Venous claudication	Entire leg, but usually worse in the thigh and groin	Tight, bursting pain	After walking	Subsides slowly	Relief speeded by elevation	History of iliofemoral deep venous thrombosis, signs of venous congestion, edema
Venous compartment syndrome	Calf muscles	Tight, bursting pain	After much exercise (e.g., jogging)	Subsides very slowly	Relief speeded by elevation	Typically, heavily muscled athletes
<b>Neurologic Conditions</b>						
Nerve root compression (e.g., herniated disk)	Radiates down leg, usually posteriorly	Sharp lancinating pain	Soon, if not immediately after onset	Not quickly relieved (also often present at rest)	Relief may be aided by adjustment of back position	History of back problems
Neurospinal root compression	Hip, thigh, buttocks (follows dermatome)	Weakness more than pain	After walking or standing for some time	Relieved by stopping only if position changed	Relieved by lumbar spine flexion (sitting or stooping forward)	Common history of back problems; provoked by increased intra-abdominal pressure
<b>Orthopedic Conditions</b>						
Hip arthritis	Hip, thigh, buttocks	Aching discomfort	After variable degree of exercise	Not quickly relieved (and may be present at rest)	Patient is more comfortable sitting with weight taken off legs	Variable; may relate to activity level, weather changes

mucinous degeneration of the artery<sup>17,18</sup> (see Ch. 144, Non-Atherosclerotic Popliteal Artery Diseases). Another condition that can be seen in younger patients is chronic compartment syndrome, an overuse syndrome that is often symmetric and bilateral (see Ch. 196, Chronic Exertional Compartment Syndrome). The most common complaints are muscle cramping and swelling, with focal paresthesias on the plantar or dorsal aspect of the foot. The pain or discomfort is associated with tightness in the calf and is precipitated by exercise. The patient is often an athlete or a runner with large calf muscles. Muscle swelling, increased compartment pressure, and impaired venous outflow constitute a vicious circle. The pain usually starts after considerable exercise and does not quickly subside with rest.

### Rest Pain

Progressive, frequently multilevel atherosclerotic obstructive disease results in ischemic rest pain. In the absence of acute embolic or thrombotic arterial occlusion, the onset of symptoms is gradual. In most cases, the patient will have a history of claudication. With injury or minor trauma, the patient may have associated nonhealing ulcers. Pain at rest represents a significant decrease in circulation and involves the most distal aspect of the lower extremity, which is farthest from the central source of circulation and blood flow. The forefoot and digits are most commonly involved. In the absence of acute arterial occlusion, patients do not have pain in the thigh or calf at rest. The symptoms are classically relieved with dependency because gravity tends to facilitate circulation. The symptoms are aggravated if

**TABLE 19.2**

Answers to the Rose Questionnaire by Patients with or without Arthritis, with a Low Ankle–Brachial Index and Exertional Leg Pain, but without Positive Rose Questionnaire Findings for Intermittent Claudication ( $N = 234$ )

Question	THOSE WITHOUT ARTHRITIS ( $N = 73$ )		THOSE WITH ARTHRITIS ( $N = 156$ )		<i>P</i> Value
	Number	Percentage	Number	Percentage	
Do you have pain in either leg on walking?	73	100	156	100	—
Does the pain begin when standing still or sitting? Answer = No	57	78.1	60	38.5	0.001
Do you get this pain in your calf/calves? Answer = Yes	55	75.3	118	76.1	0.897
Do you get it if you walk uphill or hurry? Answer = Yes	55	82.1	86	72.3	0.133
Do you get it when you walk at an ordinary pace on the level? Answer = Yes	46	62.2	97	65.5	0.620
Does it ever disappear while walking? Answer = No	22	29.7	76	50.7	0.003
What do you do if you get it while walking? Answer = Stop or slow down	54	72.0	123	83.7	0.041
What happens to the pain if you stand still? Answer = Relieved in 10 minutes or less	59	95.2	82	72.6	0.001

From Newman AB, Naydeck BL, Sutton-Tyrrell K, et al. For the Cardiovascular Study Research Group. The role of comorbidity in the assessment of intermittent claudication in older adults. *J Clin Epidemiol*. 2001;54:294–300.

the patient lies down and elevates the extremity, which further increases the work of pushing blood against gravity to the foot. Patients will complain that the pain awakens them at night or develops soon after lying down. It is not uncommon for patients to be unable to describe the character of the pain. It is easiest to quantify the severity of rest pain relative to the sleep that patients are able to obtain. Early in the course, patients may awaken only occasionally and are able to get back to sleep after sitting up or walking about the room. With time, patients must sleep with their foot constantly hanging over the edge of the bed.

The clinical distinction between rest pain and tissue loss – which represent the two clinical conditions described as critical limb ischemia – is a matter of constant debate. While both syndromes require urgent attention, the clinical risk for amputation implied by the latter is presumed to be much higher. However, the magnitude of this difference remains a topic of discussion.

### Conditions Mimicking Rest Pain

Clinicians should note, and investigate, other etiologies of leg pain, especially when noninvasive tests fail to reveal evidence of PAD. As shown in several examples below, inconsistencies in the history can suggest an alternative diagnosis.

### Diabetic neuropathy

Diabetic patients are prone to a distal arterial occlusive process that frequently involves the tibial and digital arteries and can result in severe ischemia and pain at rest. Diabetic patients

can also have associated peripheral neuropathy (see Ch. 12, Diabetes). Diabetic neuropathy can involve the forefoot and digits, and is often described as a burning pain, hyperesthesia, or a “pins and needles” sensation. A careful history should permit differentiation between ischemic rest pain and neuropathy because neuropathic pain is constant and unrelieved by dependency.

### Complex regional pain syndrome

Complex regional pain syndrome (or reflex sympathetic dystrophy or causalgia) is described in detail in Chapter 192 (Complex Regional Pain Syndrome). Often the pain originates after soft tissue or nerve injury. Pain is the most common and prominent feature. The pain is frequently burning and can be worse in the distal aspects of the extremity.

### Upper Extremity Effort Discomfort

Effort discomfort involving the upper extremity can be associated with stenosis or occlusion of the subclavian or axillary arteries. Like claudication, symptoms are induced by exercise and relieved by rest. A careful history should allow the examiner to make a distinction between symptoms related to arterial disease and those associated with thoracic outlet syndrome (see Ch. 125, Thoracic Outlet Syndrome: Arterial). In neurogenic thoracic outlet syndrome, the nerve roots that form the brachial plexus and its trunks are compressed within the scalene triangle (see Ch. 124, Thoracic Outlet Syndrome: Neurogenic). While the diagnosis of these patients can be especially difficult, careful attention to physical exam and a reliable history will

add to the ability to decide whether or not surgical treatment is the best course.

## PHYSICAL EXAMINATION IN PATIENTS WITH ARTERIAL DISEASE

Regardless of the suspected vascular pathology, physical examination of an individual with suspected arterial disease should be complete because of the systemic nature of the atherosclerotic process underlying the arterial disease.

### Inspection

The examination begins with the observation or inspection of the extremities. Significant PAD can be associated with atrophy of the calf muscles; loss of hair growth over the lower part of the leg and foot is also a common sign of arterial insufficiency, as is thickening of the nails. With more advanced changes, atrophy of the skin is seen; there is a decrease in subcutaneous tissue, and the skin assumes a fragile, shiny appearance. With severe ischemia, dependent rubor is observed, and the distal part of the leg, the foot, and the digits may appear reddish. On elevating the lower extremity, the rubrous appearance is replaced with pallor.

### *Ischemic Ulcers*

With increasing ischemia, the formation of ischemic ulcers can be observed. These ulcers are small and circinate, with pale, grayish granulation tissue in the base. They are noted specifically on the toes, heels, or fingertips, and if found more proximally, they are usually secondary to trauma. When examining the foot and digits for ischemic ulcers, care should be taken to examine between the toes because skin breakdown and small fissures can frequently begin in these intertriginous areas. Ischemic ulcers are usually painful and can progress to tissue necrosis and frank gangrene. Gangrene can consist of dry eschar, or be “wet” due to purulent or serous drainage at the margins of the eschar. Table 19.3 provides a model that can be used to describe and document ischemic ulcers and wounds in a uniform fashion.

### *Livedo Reticularis*

Close examination of the skin may reveal abnormalities, such as livedo reticularis, which is a discoloration of the skin consisting of macular, violaceous, connecting rings that form a netlike or lacelike pattern.<sup>19</sup> Decreased flow leading to hypoxia and collateral formation are thought to cause the cutaneous findings. Livedo reticularis can be due to PAD and be found in areas of ischemia. More often it is secondary to vasculitis, calciphylaxis, atheroemboli, hyperviscosity syndromes, endocrine abnormalities, infection, or any combination of these causes. In these latter forms, the lesions are usually more diffuse. In situations in which the microcirculation is affected, splinter hemorrhages, focal areas of cyanosis, or punctate violaceous lesions can be indicative of microemboli. These lesions can often be multiple, but they can also occur in single form. The lesions

**TABLE 19.3** Documentation of Wound Characteristics

Characteristic	Observations to be Documented
Wound size	Length, width, depth, area, volume
Undermining	Presence, location, measurement
Appearance	Granulation tissue, sloughing, necrotic eschar, friability
Exudate	Amount, color, type (serous, serosanguineous, sanguineous, purulent), odor
Wound edge	Presence of maceration, advancing epithelium, erythema, even, rolled, ragged

From Lawrence PF, Caswell DR. The wound care center and limb salvage. In: Moore WS, ed. *Vascular and Endovascular Surgery. A Comprehensive Review*. 7th ed. Philadelphia: Saunders Elsevier; 2006:876–889.

are generally small in overall diameter and are frequently found to be painful.

### *Acrocyanosis*

While a precise definition of acrocyanosis remains elusive, it is a generalized term used to describe painless, symmetric, cyanotic discoloration of the hands, feet, and occasionally face and central portions of the body, such as the tips of the ears or nose. Episodes of acrocyanosis are often triggered by cold exposure. Distinction from Raynaud’s-like phenomena is difficult to discern (see Ch. 142: Raynaud’s Phenomenon).

### Pulse Examination

Palpation of pulses should be performed in a relatively consistent manner and should be complete. Comparing a pulse with that in the contralateral extremity can demonstrate important relative differences. In addition to pulses in the neck and the upper and lower extremities, the abdominal aortic pulse also should be assessed. The carotid pulse can best be palpated in the midneck region, anterior to the sternocleidomastoid muscle. Superficial temporal artery pulses should also be documented, particularly when evaluating temporal arteritis. The subclavian pulse is usually found in the suprascapular fossa, and the axillary pulse is found lateral to the clavicle along the course of the deltopectoral groove or in the axilla. Upper extremity pulses are examined in the antecubital fossa and at the wrist. Both the brachial and radial pulses can generally be felt with superficial palpation. The ulnar pulse, in contrast, does require firmer palpation because this artery follows a deeper course than the radial or brachial arteries. In the lower extremity, the common femoral, popliteal, dorsal pedal, and posterior tibial artery pulses are examined. The common femoral artery pulse can usually be found in the medial aspect of the groin, just below the inguinal ligament, and can be felt with light palpation in a thin person; deeper palpation is necessary in an obese individual. Popliteal artery pulses are more

**TABLE 19.4** Differential Diagnosis of Common Leg Ulcers

Type	Usual Location	Pain	CHARACTERISTIC			
			Bleeding With Manipulation	Lesion Characteristics	Surrounding Inflammation	Associated Findings
Ischemic ulcer	Distal, on the dorsum of the foot or toes	Severe, particularly at night; relieved by dependency	Little or none	Irregular edge; poor granulation tissue	Absent	Trophic changes of chronic ischemia; absence of pulses
Neurotrophic ulcer	Under calluses or pressure points (e.g., plantar aspect of the first or fifth metatarsophalangeal joint)	None	May be brisk	Punched out, with a deep sinus	Present	Demonstrable neuropathy
Venous stasis ulcer	Lower third of the leg (gaiter area)	Mild; relieved by elevation	Venous ooze	Shallow, irregular shape; granulating base; rounded edges	Present	Lipodermatofibrosis, pigmentation

**TABLE 19.5** Characterization of Areas of Ulceration and Tissue Loss

Ulcer Location	Ulcer Etiology	Clinical Appearance	Treatment
Toes, distal forefoot	Arterial insufficiency	Dry/wet gangrene	Revascularization
Weight-bearing surface	Diabetic neuropathy	Callus, "heaped up"	Offloading
Medial malleolus	Venous insufficiency	Beefy red, brown staining of skin	Compression, venous intervention

difficult to palpate because they are generally located lateral to the popliteal fossa. The patient's knee should be partially flexed and relaxed to allow the examiner to palpate the pulse; firm pressure is required. The posterior tibial artery pulse is typically found in the hollow posterior to the medial malleolus, and usually gentle pressure allows adequate palpation. Increased pressure, particularly in patients with poor arterial perfusion, can obscure the pulse. The dorsal pedal pulse is generally found on the dorsum of the foot between the first and second metatarsal bones. In 10% of patients, the dorsal pedal pulse is absent congenitally. In patients with suspected popliteal artery entrapment, tibial pulses should also be evaluated during active plantar flexion of the foot or during passive dorsiflexion.

### Arterial Aneurysms

During the course of the pulse examination, the size of the artery should be assessed. Typically, an aneurysm is first suspected by a prominence of the palpated pulse. If a prominent pulse is appreciated, the artery should be further evaluated to determine whether aneurysmal dilation is present, and if it is, the size of the aneurysm should be estimated and noted. Peripheral aneurysms are most commonly found in the

popliteal, common femoral, and subclavian arteries. The abdominal aorta can be palpated in thin individuals by having them relax their abdominal musculature and then palpating deeply.

### Auscultation

After palpation, the arteries should be auscultated. Although, typically, nothing is heard on auscultation, the presence of a bruit, which is indicative of turbulent blood flow, is a marker of underlying pathology. Generally speaking, the pitch and duration of a systolic bruit are correlated with increasing severity of arterial narrowing, but it is difficult to quantify the degree of stenosis. Bruits extending into diastole may suggest the presence of an arteriovenous fistula. Although uncommon in the past, arteriovenous fistulae are being seen with increasing frequency because of the rising number of arterial catheterizations.

### Palmar Circulation

In patients with upper extremity arterial disease, it may be of value to assess the patency of the palmar arch. Typically,

circulation to the hand is supplied by both the radial and ulnar arteries. These two arteries merge to form the palmar arch. In approximately 10% of the population, the arch is congenitally incomplete. The Allen test can demonstrate the presence of an incomplete arch or occlusion of the arch. In this test, pressure is applied at the wrist to occlude the radial and ulnar arteries. The patient is asked to open and close the hand, making a fist. After several repetitions, the palmar aspect of the hand blanches and becomes pale. With release of pressure over the radial or ulnar artery, normal skin color should return within seconds.

## THE ULCERATED LEG

Chronic ulcers can be associated with arterial ischemia, venous stasis, or neuropathy (Table 19.4). The history and physical examination are critical because the causes are not mutually exclusive. A history of arterial insufficiency, including claudication and rest pain, should be sought. Ischemic ulcers and tissue loss represent the far end of the spectrum of arterial disease. Diabetics can have arterial disease and peripheral neuropathy. Neuropathy can predispose diabetic patients to neurotrophic ulcers over the weight-bearing prominences of the plantar surface of the foot. Venous stasis disease can result in characteristic ulcerations, but associated arterial disease can affect healing and influence treatment. All areas of ulceration and tissue loss should be fully characterized with respect to location and size (Table 19.5).

### Ischemic Ulcers

Ischemic ulcers are usually painful, and there is likely to be typical ischemic rest pain in the distal part of the forefoot that occurs nocturnally and is relieved by dependency. At first, these ulcers may have irregular edges, but when chronic, they are more likely to be “punched out.” They are commonly located distally over the dorsum of the foot or toes but may occasionally be pretibial. The ulcer base usually consists of poorly developed, grayish granulation tissue. The surrounding skin may be pale or mottled, and the previously described signs of chronic ischemia are invariably present. Notably, the usual signs of inflammation that one would expect surrounding such a skin lesion are absent, because it is the lack of adequate circulation to provide the necessary inflammatory response for healing that underlies ischemic ulcers. For the same reason, probing or debriding the ulcer causes little bleeding.

### Neuropathic Ulcers

Neuropathic ulcers are completely painless but bleed with manipulation. They are deep and indolent and are often surrounded not only by acute but also by chronic inflammatory reaction and callus. Their location is typically over pressure

points or calluses (e.g., the plantar surface of the first or fifth metatarsophalangeal joint, the base of the distal phalanx of the great toe, the dorsum of the interphalangeal joints of toes with flexion contractures, or the callused posterior rim of the heel pad). The patient generally has long-standing diabetes with a neuropathy characterized by patchy hypoesthesia and diminution of positional sense, two-point discrimination, and vibratory perception.

### Stasis Ulceration

Ischemic ulcers should be differentiated from venous stasis ulcers secondary to ambulatory venous hypertension. These ulcers are typically located within the gaiter area, most commonly near the medial malleolus, and are usually larger than the other types of ulcers and irregular in outline, but also shallower and with a moist granulating base. The ulcer is almost invariably surrounded by a zone containing some of the hallmarks of chronic venous insufficiency – pigmentation and inflammation (“stasis dermatitis”), lipodermatofibrosis, and cutaneous atrophy (see Ch. 20, Clinical Evaluation of the Venous and Lymphatic Systems).

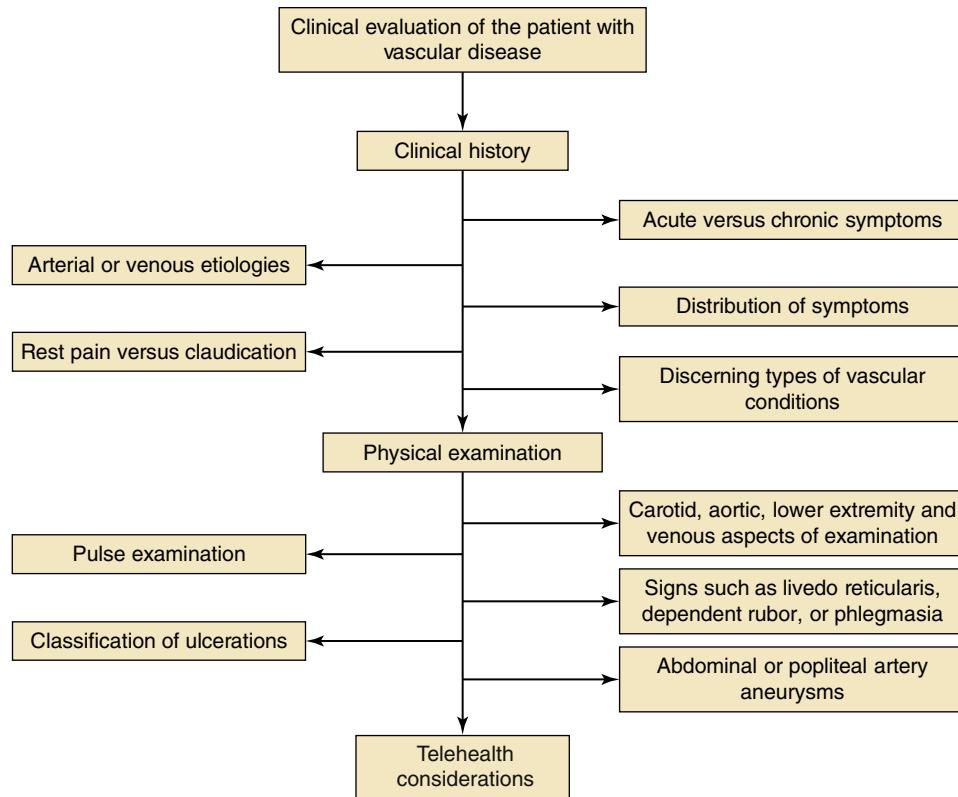
### Other Types of Ulcers

More than 95% of all chronic leg or foot ulcers fit into one of the previously described recognizable types. However, leg ulcers may also be produced by vasculitis and hypertension. Vasculitis frequently produces multiple punched-out ulcers and an inflamed indurated base, which, on biopsy, suggests fat necrosis or chronic panniculitis. Hypertensive ulcers represent focal infarcts and are very painful. They may be located around the malleoli, particularly laterally. Long-standing ulcers that are refractory to treatment may represent underlying osteomyelitis or a secondary malignant lesion. Finally, most patients with ulcers identify trauma as an initiating cause. In diabetics, ulcers may also be related to poorly fitting shoes that result in persistent irritation or trauma, or uneven weight distribution on the plantar surface of the foot.

### Ulcer Assessment: What's Next

The presence of an ulcer can be a risk factor for amputation. However, as outlined above, there is significant heterogeneity in ulcer types, and with it, heterogeneity in amputation risk. Categorizing and assessing ulcers has proven challenging, and several wound assessment mechanisms beyond physical examination have evolved.<sup>20,21</sup> The testing and validation of these assessment systems, which usually involve digital photography, electronic health records, and a rating system, is an active area of investigation. These aspects can help to improve not only in-person visits, but telehealth visits as well.

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A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com).

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# Clinical Evaluation of the Venous and Lymphatic Systems

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## ANATOMIC CONSIDERATIONS

The anatomy of the veins and lymphatics provides the basis for understanding the pathophysiology of common disease states. With the primary purpose of the veins to return blood to the heart in a unidirectional fashion and for the lymphatics to carry excess interstitial fluid and particulate matter back to the central circulatory system, any interruption or alteration in normal flow patterns forms the basis for venous and lymphatic pathology.

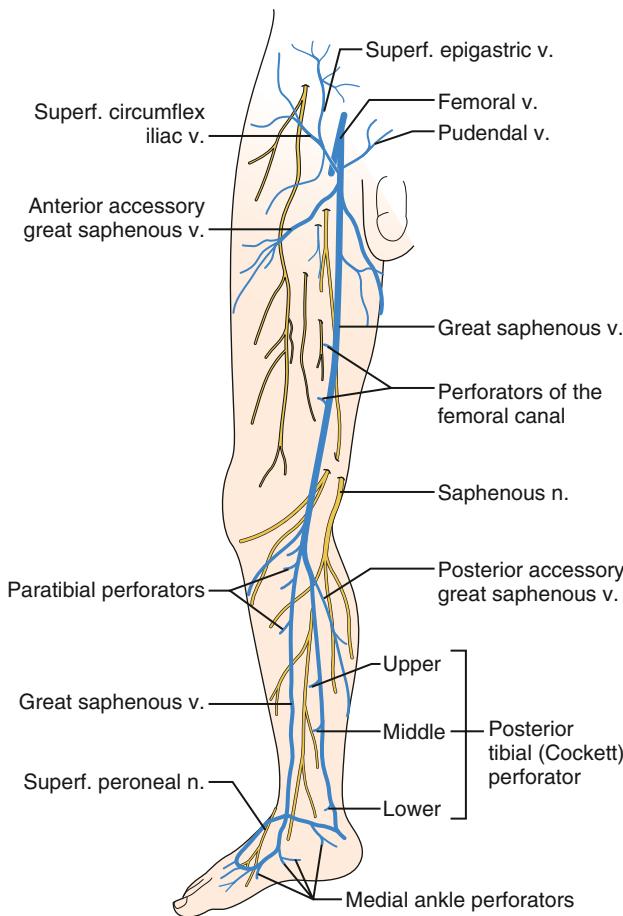
## **Deep Veins of the Lower Extremity**

The deep veins of the leg are bounded within their muscular compartments and enveloping fascia; they run together with the corresponding arterial and lymphatic structures.<sup>1</sup> The anterior tibial, posterior tibial, and peroneal veins are generally paired and coalesce to form the popliteal vein or veins, which may also be paired. The popliteal vein passes superiorly through the adductor canal, becoming the femoral vein (previously referred to as the superficial femoral vein), which then merges

with the deep femoral vein to form the common femoral vein. Cranial to the inguinal ligament, the common femoral vein becomes the external iliac vein. The external and internal iliac veins merge to form the common iliac vein. The left common iliac vein passes deep to the right common iliac artery and joins the right common iliac vein to become the inferior vena cava.

## Superficial Veins of the Lower Extremity

The superficial veins, lying above the muscular fascia, are bounded superficially by the saphenous fascia. The great saphenous vein originates at the level of the ankle and continues medially to the saphenofemoral junction, where it joins with the common femoral vein. Accessory saphenous tributaries arise from the saphenofemoral junction in variable anteromedial and anterolateral distributions (Fig. 20.1). The small saphenous vein originates over the lateral ankle, lying above the muscular compartment, and is bounded by saphenous fascia superficially. It drains into the popliteal vein at the sapheno-popliteal junction (Fig. 20.2). Two anatomically important veins are the intersaphenous vein (often referred to as the vein of Giacomini), connecting the great and the small saphenous veins, and the posterior accessory great saphenous vein, draining the subcutaneous tissue and skin overlying the medial calf.<sup>2</sup>



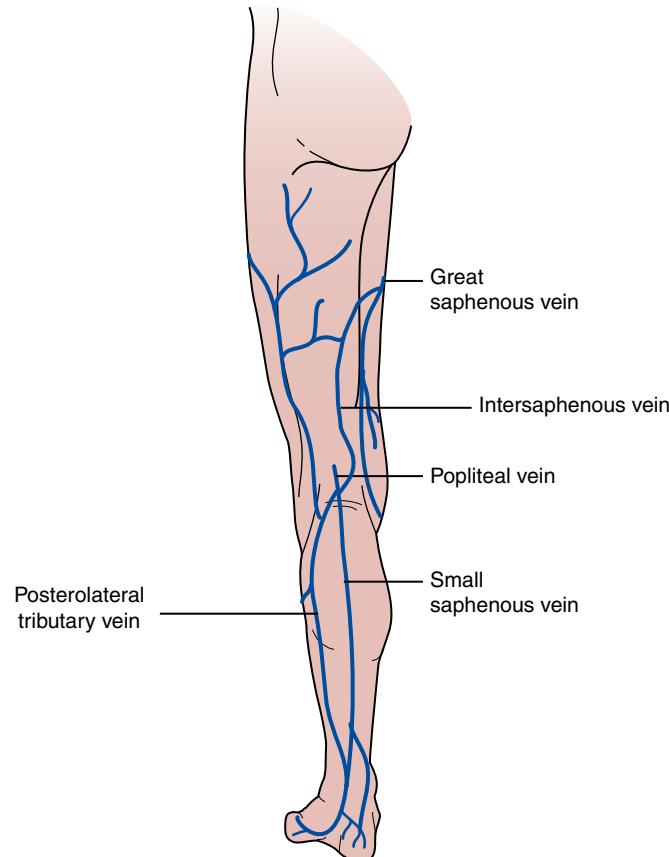
**Figure 20.1** Anatomy of medial superficial and perforating veins of the leg. (From Rutherford, 6th edition, Fig. 158–151, p. 2269.)

Perforating veins can be found along the length of the lower extremity, with the majority located below the knee.<sup>3,4</sup> These veins traverse the muscular fascia and connect the deep and superficial veins, with flow normally occurring from the superficial veins into the deep venous system. These perforators (Fig. 20.3) are located from the level of the heel to the upper thigh along the medial leg in a narrow band and are often described based on named anatomic location or distance from the proximal medial malleolus.

The remaining veins lying above the muscular fascia and underneath the dermis are best described as communicating veins, which form a variable network that interconnects the named superficial veins.

## Deep Veins of the Upper Extremity

Like those veins in the lower extremity, the deep veins of the upper extremity run in a paired fashion along with the radial and ulnar arteries, coalescing to form the brachial veins at the level of the antecubital fossa where they are bounded by the bicapital aponeurosis. Traversing the upper arm, the brachial vein



**Figure 20.2** The small saphenous vein dominates the posterolateral superficial venous drainage and originates in the dorsal venous arch. At the posterolateral ankle, it is intimately associated with the sural nerve. Note the important posterolateral tributary vein and the posterior thigh vein, which ascend and connect the small saphenous venous system with the great saphenous venous system. (From Mozes G, Carmichael SW, Gloviczki P. Development and anatomy of the venous system. In: Gloviczki P, Yao JST, eds. *Handbook of Venous Disorders*. 2nd ed. London: Arnold; 2001:11–24. From Rutherford, 6th edition, Fig. 158–152, p. 2269.)

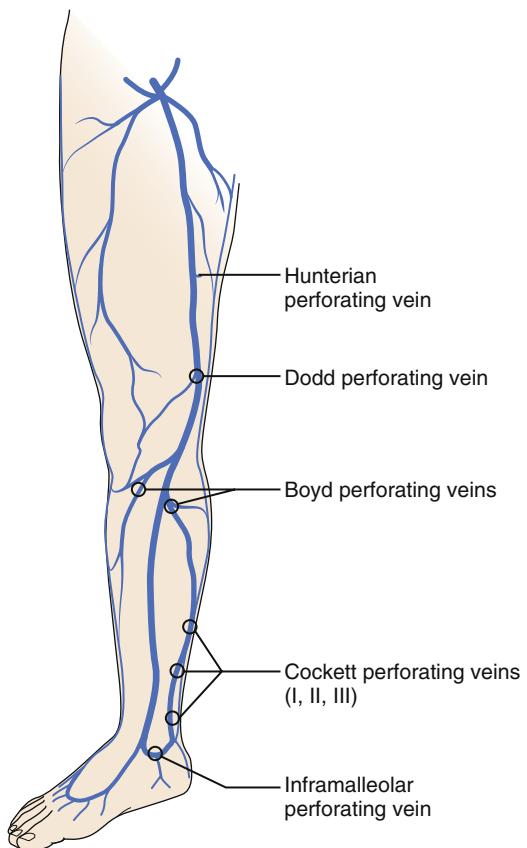
or veins become the axillary vein or veins at the lower margin of the teres major muscle and subsequently the subclavian vein at the lateral edge of the first rib.<sup>5</sup>

## Superficial Veins of the Upper Extremity

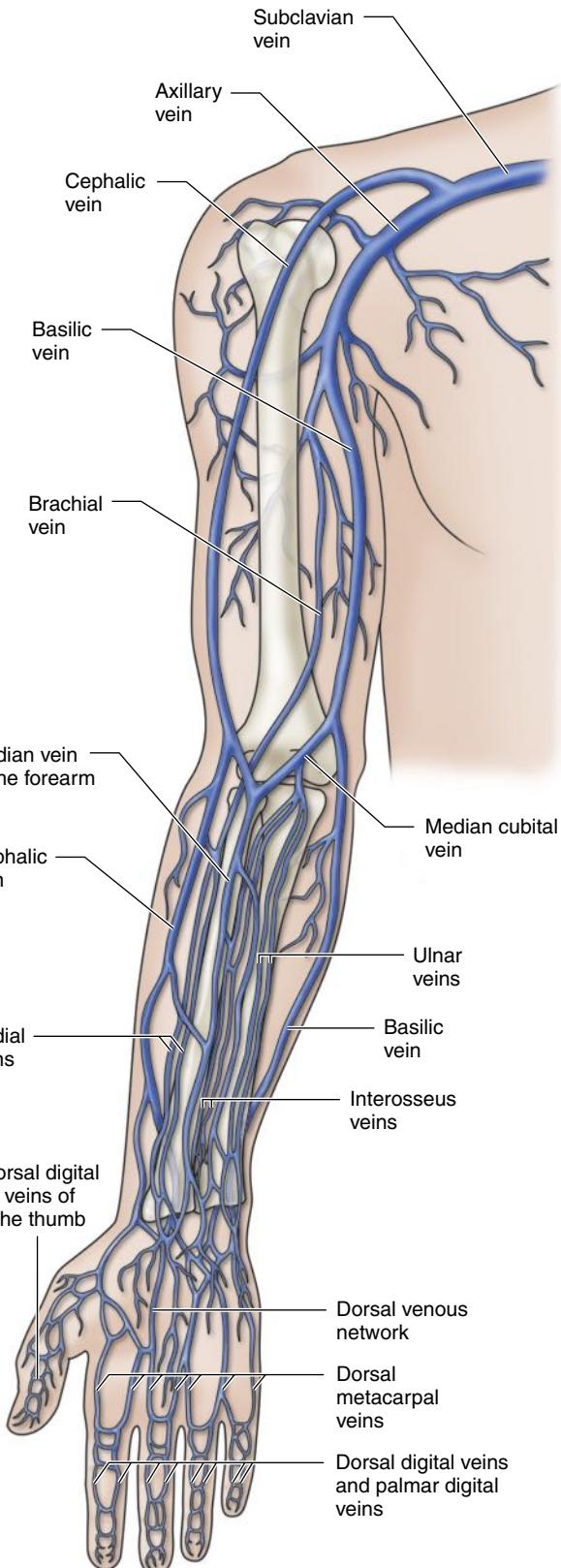
Superficial veins arising at the wrist include the cephalic and basilic veins, which lie above the muscular fascia underneath the skin and invariably become invested in superficial fascia at the level of the middle forearm. The cephalic vein continues along the lateral aspect of the arm, coursing to the level of the deltectoral groove and finally joining the subclavian vein. Similarly, the basilic vein lies medially at the level of the wrist, beneath the skin, and courses to the level of the upper arm piercing the muscular fascia to join the brachial or axillary vein (Fig. 20.4).

## Lymphatics of the Lower Extremity

In the lower extremity the lymphatics can be divided into vessels and nodes. There are two sets of lymphatic vessels, which correspond to the deep and superficial veins. The vessels parallel the corresponding veins. There is a significantly increased number of superficial lymphatic vessels when compared with the deep



**Figure 20.3** The location of the most important perforating veins associated with the great saphenous vein is shown. The Cockett and inframalleolar perforating veins are actually separate from the great saphenous system. The Boyd perforating vein is constantly present, but it may drain the saphenous vein or its tributaries. Perforating veins in the distal third of the thigh are referred to as “Dodd perforators,” whereas those in the middle third of the thigh are referred to “Hunterian perforators.” (From Rutherford, 6th edition, Fig. 157–152, p. 2252.)



**Figure 20.4** Schematic drawing of the venous anatomy of the right upper extremity. (From Uflacker A, Guimaraes M. *Uflacker's Atlas of Vascular Anatomy: An Angiographic Approach*, 3rd ed. (Fig 16-1A, p. 532). Wolters-Kluwer.)

lymphatic vessels. The vessels drain into lymphatic glands or lymph nodes. These are primarily found in the popliteal region, where it is common to see five to seven of them embedded within the popliteal fossa. In the inguinal region 10 to 20 nodes are present and are primarily found in the femoral triangle (Fig. 20.5).<sup>6</sup>

### Lymphatics of the Upper Extremity

The lymphatic vessels of the upper extremity also follow the superficial and deep vascular structures. As in the lower extremity, the lymph node numbers increase moving proximally, with a significant number at the level of the axillary and supraclavicular region (Fig. 20.6).

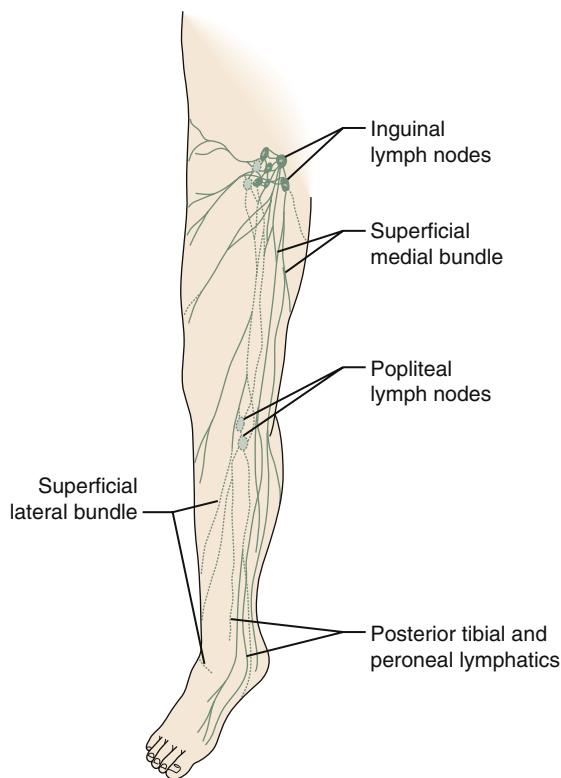
## THE CLINICAL EVALUATION

Most venous and lymphatic problems can be approached in an organized and sequential fashion. First, the presenting complaint should be determined; physical examination should correlate with the presenting history and should also provide a bridge to the pathophysiology of the disease process. When the history and physical examination have been completed, diagnostic studies can be ordered, if necessary, to further localize the disease or quantify the extent of the process. Therapy is ultimately driven by the natural history of the disease process and its impact on the patient's quality of life as well as the patient's risk factors and functional status. A relatively benign natural history, or significant and unmodified patient risk factors, may indicate an initial course of medical management, risk-factor

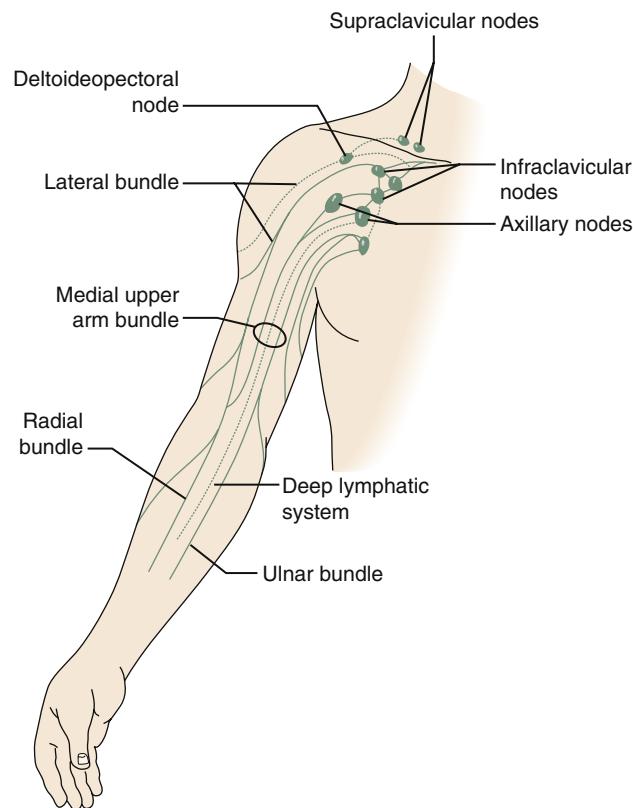
modification, and observation; threat of significant hemodynamic consequences or tissue loss may indicate the need for a more aggressive intervention.

Typically, presenting symptoms can be broadly classified into the following categories: pain; weakness; neurosensory complaints including warmth, coolness, numbness, and hypersensitivity; discoloration; swelling; tissue loss and ulceration; and varicosities. The history should attempt to identify and characterize the location of the symptoms (unilateral, bilateral, proximal, distal); acuity of onset (sudden/gradual); duration; character, including frequency of symptoms and temporal patterns (continuous, intermittent); course or progression (better, worse, unchanged); and factors that aggravate and ameliorate the symptoms, including position, activity, temperature, menses, vibration, and pressure.

The physical examination should progress from observation and inspection to palpation. On observation, the extremity should be assessed for evidence of skin changes, including atrophy, cyanosis or mottling, pallor, rubor, lipodermatosclerosis, and ulcerations. The presence and location of edema should be identified and quantified by measurement of circumference. Tissue loss and ulceration should be noted and fully described, including the location, size and depth, as well as presence of associated cellulitis and inflammation. On initial palpation, changes in temperature and sensation should be noted and compared with the contralateral extremity. All accessible pulses should be evaluated. At a minimum, pulses should be classified as absent, decreased, or normal; with use of the Doppler when



**Figure 20.5** The lymphatic system of the lower extremity. (From Rutherford, 6th edition, Fig. 169.4, p. 2434.)



**Figure 20.6** The lymphatic system of the upper extremity. (From Rutherford, 6th edition, Fig. 169.6, p. 2434.)

pulses are nonpalpable, especially in patients with marked edema, to confirm adequate arterial inflow.

The severity of venous diseases can be classified using multiple models that have been shown to be of value for clinical and research purposes. These include anatomic location (Table 20.1); the Clinical, Etiologic, Anatomic, Pathophysiologic (CEAP) classification system (Table 20.2); the Venous Clinical Severity Score (VCSS) (Table 20.3); the Venous Segmental Disease Score (VSDS) (Table 20.4); and the Venous Disability Score

**TABLE 20.1** Segmental Localization of Chronic Venous Disease of the Lower Extremity

Number	Segment
	Superficial veins (AS1–5)
1	Great saphenous vein
2	Above knee
3	Below knee
4	Small saphenous vein
5	Nonsaphenous
	Deep veins (AD6–16)
6	Inferior vena cava
	Iliac
7	Common
8	Internal
9	External
10	Pelvic: gonadal, broad ligament
	Femoral
11	Common
12	Deep
13	Superficial*
14	Popliteal
15	Tibial (anterior, posterior, or peroneal)
16	Muscular (gastrocnemius, soleal, other)
	Perforating veins (AP17–18)
17	Thigh
18	Calf

\*The superficial femoral vein is now referred to as the femoral vein.  
From Rutherford, 6th edition, Table 155.2, p. 2234. From Porter JM, Moneta GL. Reporting standards in venous disease: an update. International Consensus Committee on Chronic Venous Disease. *J Vasc Surg*. 1995;21:635–645; with permission from Society for Vascular Surgery.

**TABLE 20.2**

Overall Classification System for Chronic Venous Insufficiency: Clinical, Etiologic, Anatomic, Pathophysiologic (CEAP)

Category	Finding	Classification
Clinical	Asymptomatic	C0
	Telangiectasias, reticular veins, malleolar flare	C1
	Varicose veins	C2
	Recurrent varicose veins	C2r
	Edema, no skin changes	C3
	Changes in the skin and subcutaneous tissue secondary to CVD	C4
	Pigmentation or eczema	C4a
	Lipodermatosclerosis and atrophie blanche	C4b
	Corona phlebectatica	C4c
	Skin changes as above with healed ulcer	C5
Etiologic	Skin changes as above with active ulcer	C6
	Recurrent active venous ulcer	C6r
	Primary	Ep
	Secondary	Es
	Secondary – intravenous	Esi
Anatomic	Secondary – extravenuous	Ese
	Congenital	Ec
	<b>Superficial</b>	<b>As</b>
	Reticular veins	As Ret
	Great saphenous vein above knee	As GSVA
	Great saphenous vein below knee	As GSVb
	Small saphenous vein	As SSV
	Anterior accessory vein	As AASV
	Nonsaphenous vein	As NSV
	<b>Deep</b>	<b>Ad</b>
	Inferior vena cava	Ad IVC
	Common iliac vein	Ad CIV
	Internal iliac vein	Ad IIIV
	External iliac vein	Ad EIV
	Pelvic veins	Ad PELV
	Common femoral vein	Ad CFV
	Femoral vein	Ad FV
	Popliteal vein	Ad PV
	Crural (tibial) vein	Ad TIBV
	Peroneal vein	Ad PRV
	Anterior tibial vein	Ad ATV
	Posterior tibial vein	Ad PTV
	Muscular veins	Ad MUSV
	Gastrocnemius vein	Ad GAV
	Soleal vein	Ad SOV
	<b>Perforator</b>	<b>Ap</b>
	Thigh perforator vein	Ap TPV
	Calf perforator vein	Ap CPV
	<b>No venous anatomic location identified</b>	<b>An</b>
Pathophysiologic	Reflux	Pr
	Obstruction	Po
	Reflux and obstruction	Pro
	No pathophysiology identified	Pn

Modified from Rutherford, 9th edition, Table 19.2, p. 203 and Lurie et al.<sup>8</sup>

**TABLE 20.3** Venous Severity Scoring: The Venous Clinical Severity Score

Attribute	Absent: 0	Mild: 1	Moderate: 2	Severe: 3
Pain	None	Occasional; not restricting activity or requiring analgesics	Daily; moderate activity limitation; occasional analgesics	Daily; severely limiting activities or requiring regular use of analgesics
Varicose veins <sup>a</sup>	None	Few, scattered: branch varicose veins	Multiple: GS varicose veins confined to calf or thigh	Extensive: thigh and calf or GS and LS distribution
Venous edema <sup>b</sup>	None	Evening ankle edema only	Afternoon edema above ankle	Morning edema above ankle and requiring activity change, elevation
Skin pigmentation <sup>c</sup>	None or focal, low-intensity (tan)	Diffuse, but limited in area and old (brown)	Diffuse over most of gaiter distribution (lower $\frac{1}{3}$ of leg) or recent pigmentation (purple)	Wider distribution (above lower $\frac{1}{3}$ of leg) and recent pigmentation
Inflammation	None	Mild cellulitis, limited to marginal area around ulcer	Moderate cellulitis, involving most of gaiter area (lower $\frac{1}{3}$ of leg)	Severe cellulitis (lower $\frac{1}{3}$ of leg and above) or significant venous eczema
Induration	None	Focal, circummalleolar (<5 cm)	Medial or lateral, less than lower	Entire lower $\frac{1}{3}$ of leg or more
No. of acute ulcers	0	1	2	>2
Active ulceration	No	Yes; <3 months	Yes; >3 months, <1 year	Yes; not healed > 1 year duration
Active ulcer, size	No	Yes; <2 cm	Yes; 2–6 cm	Yes; >6 cm (diameter)
Compressive therapy	Not used or not compliant	Intermittent use of stockings	Patient wears elastic stockings most days	Full compliance: stockings and compliant elevation

<sup>a</sup>“Varicose” veins must be >4 mm in diameter to qualify so that differentiation is ensured between C1 and C2 venous disease.

<sup>b</sup>Presumes venous origin from characteristics (e.g., brawny [not pitting or spongy] edema), with significant effect of standing/limb elevation and/or other clinical evidence of venous etiology (i.e., varicose veins, history of deep venous thrombosis). Edema must be regular finding (e.g., daily occurrence). Occasional or mild edema does not qualify.

<sup>c</sup>Focal pigmentation over varicose veins does not qualify.

GS, greater saphenous; LS, lesser saphenous.

From Rutherford, 6th edition, Table 155.3, p. 2235. Modified from Rutherford RB, Padberg FT, Comerota AJ, et al. Venous severity scoring: an adjunct to venous outcome assessment. *J Vasc Surg*. 2000;31:1307–1312; with permission from Society for Vascular Surgery.

(VDS) (Table 20.5).<sup>7–9</sup> These various classification schemes are being increasingly used in clinical practice, and nationally for registry documentation. The Villalta (Table 20.6), Ginsberg, Brandjes, Windmer, CEAP, and Venous Clinical Severity Score models were evaluated by Soosainathan et al.,<sup>10</sup> who concluded that the Villalta score, combined with a venous disease-specific quality-of-life measure were the preferred tools to characterize the post-thrombotic syndrome. Table 20.7 outlines available chronic venous disease-specific and health-related quality-of-life measures.

## Venous Obstruction

Veins are normally patent and competent, with functioning valves. Pathologically, intraluminal thrombus can partially or completely obstruct a vein. Venous obstruction can remain asymptomatic, often associated with isolated tibial vein thrombosis, or can present with a symptomatic painful, swollen extremity. The latter is frequently associated with progression of the obstructing thrombus proximally. Untreated thrombosis, initially with minimal symptoms, can potentially lead to phlegmasia cerulea dolens and rarely limb loss.

Symptoms can be associated with compression, acute or chronic venous thrombosis, or postobstructive valvular

incompetence and venous reflux.<sup>11</sup> Isolated venous obstruction secondary to anatomic compression, such as that associated with May–Thurner syndrome, can result in mild to incapacitating swelling.

## Deep Venous Thrombosis

Patients with deep venous thrombosis (DVT) can present with varying symptoms and signs, depending on the extent of obstruction, the degree of inflammatory reaction, the location and anatomic extent of the obstruction, and associated comorbidities. DVT most commonly presents with unilateral swelling, discomfort, and a sense of fullness or pressure in the affected extremity. The symptoms are acute in onset and the pain is often characterized as an aching discomfort. There may be a sensation of tightness or heaviness. Patients will note that the symptoms are exacerbated with ambulation or when the legs are kept in a dependent position. Leg elevation, however, will often relieve the discomfort. Hospitalized patients with DVT can be asymptomatic, and approximately half of nonhospitalized patients presenting with classic symptoms suggestive of DVT will not have venous pathology.<sup>12</sup>

In assessing the patient with suspected DVT, it is most important to determine any predisposing risk factors that may

**TABLE 20.4**

Venous Severity Scoring: The Venous Segmental Disease Score (Based on Venous Segmental Involvement with Reflux or Obstruction<sup>a</sup>)

Reflux <sup>b</sup> Score	Vein(s)	Obstruction <sup>b,c</sup> Score	Vein(s)
1/2	Small saphenous	0 <sup>d</sup>	
1	Great saphenous	1	Greater saphenous (only if thrombosed from groin to below knee)
1/2	Perforators, thigh	0 <sup>d</sup>	
1	Perforator, calf	0 <sup>d</sup>	
2	Calf veins, multiple (posterior tibial alone = 1)	1	Calf veins, multiple
2	Popliteal vein	2	Popliteal vein
1	Femoral vein	1	Femoral vein
1	Profunda femoris vein	1	Profunda femoris vein
1	Common femoral vein and above <sup>d</sup>	2	Common femoral
	1	Iliac vein	
	1	Inferior vena cava	
10	Maximum reflux score	10	Maximum obstruction score <sup>e</sup>

<sup>a</sup>As determined by appropriate venous imaging (phlebography or duplex ultrasonography scan). Although some segments may not be routinely studied in some laboratories (e.g., profunda femoris and tibial veins), points cannot be awarded on the basis of presumption without scanning of the segments for obstruction or reflux.

<sup>b</sup>Reflux means that all the valves in that segment are incompetent. Obstruction means there is total occlusion at some point in the segment or >50% narrowing of at least half of the segment. Most segments are assigned 1 point, but some segments have been weighted more or less to fit with their perceived significance (e.g., increasing points for common femoral or popliteal obstruction and for popliteal and multiple calf vein reflux and decreasing points for lesser saphenous or thigh perforator reflux). Points can be assigned for both obstruction and reflux in the same segment; this is uncommon but can occur in some post-thrombotic states, potentially giving secondary venous insufficiency higher severity scores than primary disease.

<sup>c</sup>The excision, ligation, or traumatic obstruction of deep venous segments counts toward obstruction points just as much as their thrombosis.

<sup>d</sup>Normally there are no valves above the common femoral vein, so no reflux points are assigned to them. In addition, perforator interruption and saphenous ligation/excision do not count in the obstruction score, but as a reduction of the reflux score.

<sup>e</sup>Not all of the 11 segments can be involved in reflux or obstruction; 10 is the maximum score that can be assigned, and the maximum might be achieved by complete reflux at all segmental levels.

From Rutherford, 6th edition, Table 155.4, p. 2236. Adapted from Rutherford RB, Padberg FT, Comerota AJ, et al. Venous severity scoring: an adjunct to venous outcome assessment. *J Vasc Surg*. 2000;31:1307–1312; with permission from Society for Vascular Surgery.

**TABLE 20.5**

Venous Severity Scoring: The Venous Disability Score

0	Asymptomatic
1	Symptomatic but patient is able to carry out usual activities <sup>a</sup> without compressive therapy
2	Patient can carry out usual activities <sup>a</sup> only with compression and/or limb elevation
3	Patient is unable to carry out usual activities <sup>a</sup> even with compression and/or limb elevation

<sup>a</sup>Usual activities = patient's activities before onset of disability from venous disease.

From Rutherford, 6th edition, Table 155.5, p. 2236. Adapted from Rutherford RB, Padberg FT, Comerota AJ, et al. Venous severity scoring: an adjunct to venous outcome assessment. *J Vasc Surg*. 2000;31:1307–1312; with permission from Society for Vascular Surgery.

be present. Multiple risk factors can be associated with an increased threat of DVT, including advanced age; prolonged immobility, such as hospitalization or recent travel; recent surgery, pregnancy, significant trauma, cancer, a previous history of DVT, or a family history of venous thrombosis, and hypercoagulability such as seen in the recent COVID-19 pandemic<sup>13</sup> (see Ch. 40, Disorders of Coagulation: Hypercoagulable

States). The presence or absence of risk factors can markedly influence the duration of treatment and the potential need for lifelong anticoagulation.<sup>14,15</sup>

The differential diagnosis of DVT includes systemic causes of lower extremity swelling, which generally result in bilateral lower extremity edema. Congestive heart failure and cirrhosis (liver failure) are common systemic etiologies and may also be seen in patients with chronic renal insufficiency. The common denominator among systemic causes of lower extremity swelling is fluid overload or retention. The first manifestation of heart failure is progressive swelling of the legs, but it may also be associated with dyspnea and orthopnea.

Localized trauma or injury is most often associated with unilateral swelling. The differential diagnosis also includes cellulitis, muscle strain or tear, a Baker's cyst, hematoma, or dermatitis. Although the diagnosis of DVT can be suspected based on the presence of pain, swelling, and associated risk factors, noninvasive imaging remains a necessary adjunct in order to confirm a suspected diagnosis.

In attempts to improve diagnostic accuracy in the patient with suspected DVT, various models for risk stratification have been developed since the signs and symptoms of DVT are often nonspecific. The most commonly used probability model is that of Wells (Table 20.8) (see Ch. 148, Acute Lower Extremity

**TABLE 20.6** Villalta Postthrombotic Syndrome Score

Symptoms/clinical signs	None	Mild	Moderate	Severe
<b>Symptoms</b>				
Pain	0 points	1 point	2 points	3 points
Cramps	0 points	1 point	2 points	3 points
Heaviness	0 points	1 point	2 points	3 points
Paresthesia	0 points	1 point	2 points	3 points
Pruritus	0 points	1 point	2 points	3 points
<b>Clinical signs</b>				
Pretibial edema	0 points	1 point	2 points	3 points
Skin induration	0 points	1 point	2 points	3 points
Hyperpigmentation	0 points	1 point	2 points	3 points
Redness	0 points	1 point	2 points	3 points
Venous ectasia	0 points	1 point	2 points	3 points
Pain on calf compression	0 points	1 point	2 points	3 points
Venous ulcer	Absent			Present

PTS, post-thrombotic syndrome.

From Soosainathan A, Moore HM, Gohel MS, Davies MS. Scoring systems for the post-thrombotic syndrome. *J Vasc Surg*. 2013;57:254–261.

**TABLE 20.7** Quality-of-Life Assessments

Outcome Assessment	Focus on CVD	QoL Score <sup>a</sup>	Construct
SF-36	Generic, applicable to a spectrum of nonvenous and venous diseases	Ascending	36 items Physical and mental health 8 domains
AVVQ – Aberdeen Varicose Vein Questionnaire	Varicose veins, CVD	Descending	13 items Weighted scoring Patient draws varices onto template
CIVIQ – Chronic Venous Insufficiency Questionnaire	General venous	Ascending	20 items Diagnosis based on clinical and subjective symptoms; no objective confirmation of venous etiology
VEINES – Venous Insufficiency Epidemiologic and Economic Study	General venous	Ascending	35 items, 2 categories VEINES-QoL measures the effect on QoL VEINES-Sym measures symptoms
CCVUQ – Charing Cross Venous Ulcer Questionnaire	Venous ulcer	Descending	20 items Venous etiology confirmed with clinical examination and Duplex ultrasonography

<sup>a</sup>Ascending scores indicate that a higher score means a better QoL, whereas a descending score indicates that a lower score has a better QoL.

CVD, chronic venous disease; QoL, quality of life; SF-36, short form health survey (36 items).

From Rutherford, 7th edition, Table 53.3, p. 837.

Deep Venous Thrombosis: Presentation, Diagnosis, and Medical Treatment). The Wells criteria include both subjective and objective elements, resulting in a score that indicates a low, moderate, or high risk of DVT.<sup>16</sup> The Wells criteria have been prospectively validated and are in use clinically, especially in emergency departments, where routine use of vascular ultrasound is not practical and a low pretest probability is associated with only a 2% to 3% incidence of DVT. Unfortunately, the Wells scoring model still incorporates a subjective determination of alternative diagnoses, which, if present, significantly

lower the clinical probability of DVT. Meta-analysis examining the clinical diagnosis of DVT<sup>17</sup> suggests that the Wells criteria are most accurate in the identification of proximal DVT in cohorts of younger patients without a prior history of thromboembolism. Goodacre et al.<sup>18</sup> examined 18 strategies used to diagnose suspected DVT. They concluded that the optimal strategy was to discharge patients with a low or intermediate Wells score and a negative D-dimer. Ultrasound was reserved for those patients with a high Wells score or a positive D-dimer. In a report by Neher et al.,<sup>19</sup> the authors

reported that the accuracy of the D-dimer test varied with the method of analysis. The highest sensitivity was associated with the ELISA assay.

**TABLE 20.8** Stratification of Pretest Probability: The Wells Criteria

Clinical Feature	Score
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden >3 days or major surgery within 4 weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by more than 3 cm compared with the asymptomatic leg (measured 10 cm below tibial tuberosity)	1
Pitting edema (greater in the symptomatic leg)	1
Collateral superficial veins (nonvaricose)	1
Alternative diagnosis as likely as or more likely than that of deep venous thrombosis	-2

Low probability, ≤0 points; moderate probability, 1–2 points; high probability, 3 points.

From Rutherford, 6th edition, Table 148.3, p. 2151. Modified from Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *Lancet*. 1997;350:1795–1798.

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The Caprini Risk Assessment model is specific to surgical patients, factoring in clinical variables based on a point system to determine a perioperative risk of DVT, and the appropriate perioperative prophylactic measures. This assessment has been validated to be accurate in appropriate populations (Table 20.9).<sup>20,21</sup>

Regardless of the presentation or physical findings, it is essential in the initial assessment of the patient presenting with DVT to determine the cause of the thrombotic event. This allows the provider to classify the event as either a “provoked” or “unprovoked” DVT. The duration of anticoagulation is markedly altered in those patients who present with an unprovoked DVT. They are by default considered potentially hypercoagulable, even in the presence of a negative laboratory workup, and consideration for lifelong anticoagulation should be entertained. The American College of Chest Physicians has provided ongoing evidence-based guidelines for the treatment of DVT.<sup>22,23</sup>

DVT can also involve the subclavian and axillary veins in the upper extremity. Onset is typically acute and associated with swelling of the entire arm. There has always been a strong relationship between venous thrombosis and compression of the subclavian vein at the thoracic outlet due to abnormal rib, clavicle, and muscular pathology, and patients will frequently note an association with upper-body exercise and activity (see Ch. 126, Thoracic Outlet Syndrome: Venous). More recently, subclavian and axillary vein thrombosis has been increasingly associated with subclavian vein catheters placed for central access (see Ch. 150, Acute Upper Extremity and Catheter-Related Venous Thrombosis).

**TABLE 20.9** Caprini Risk Factors and Score Risk Category Association

Each risk factor = 1 point	Each risk factor = 2 points	Each risk factor = 3 points	
<ul style="list-style-type: none"> <li>Age 40–59 years</li> <li>Minor surgery planned</li> <li>BMI ≥30 kg/m<sup>2</sup></li> <li>History of prior major surgery (&lt;1 month)</li> <li>Swollen legs (current)</li> <li>Varicose veins</li> <li>Sepsis (&lt;1 month)</li> <li>Abnormal pulmonary function (COPD)</li> <li>Acute myocardial infarction (&lt;1 month)</li> <li>Congestive heart failure (&lt;1 month)</li> <li>History of IBD</li> <li>Medical patient currently at bed rest</li> </ul>	<ul style="list-style-type: none"> <li>Age 60–74 years</li> <li>Arthroscopic surgery</li> <li>Major open surgery (&gt;45 minutes)</li> <li>Laparoscopic surgery (&gt; 45 minutes)</li> <li>Prior cancer (except nonmelanoma skin cancer)</li> <li>Present cancer (except breast and thyroid)</li> <li>Confined to bed (&gt;72 hours)</li> <li>Immobilizing plaster cast</li> <li>Central venous access</li> </ul>	<ul style="list-style-type: none"> <li>Age ≥75 years</li> <li>History of VTE</li> <li>Family history of VTE</li> <li>Present chemotherapy</li> <li>Positive factor V Leiden</li> <li>Positive prothrombin 20210A</li> <li>Positive lupus anticoagulant</li> <li>Elevated anticardiolipin antibodies</li> <li>Elevated serum homocysteine</li> <li>Heparin-induced thrombocytopenia (HIT)</li> <li>Other congenital or acquired thrombophilias</li> </ul>	
<b>CAPRINI RISK CATEGORY BASED ON TOTAL RISK SCORE</b>			
For women only (1 point each)	Total Score	Category	Each risk factor = 5 points
<ul style="list-style-type: none"> <li>Pregnant or postpartum</li> <li>History of unexplained or recurrent spontaneous abortion</li> <li>Oral contraceptives or hormone replacement therapy</li> </ul>	<ul style="list-style-type: none"> <li>0–4</li> <li>5–8</li> <li>≥9</li> </ul>	<ul style="list-style-type: none"> <li>Low</li> <li>Moderate</li> <li>High</li> </ul>	<ul style="list-style-type: none"> <li>Major surgery lasting &gt; 6 hours</li> <li>Stroke (&lt;1 month)</li> <li>Elective major lower extremity arthroplasty</li> <li>Hip, pelvis, leg fracture (&lt;1 month)</li> <li>Acute spinal cord fracture or paralysis (&lt;1 month)</li> <li>Multiple traumas (&lt;1 month)</li> </ul>

BMI, Body Mass Index; COPD, chronic obstructive pulmonary disease; IBD, inflammatory bowel disease; VTE, venous thromboembolism.

From Sterling HM, Rosen AK, Hachey KJ, et al. Caprini Risk Model decreases venous thromboembolism rates in thoracic surgery cancer patients. *Ann Thorac Surg*. 2018;105:879–885.

### Physical Examination

The presence of any swelling or edema should be noted and described. Unilateral or bilateral involvement should be noted, as well as the extent of involvement (i.e., is the entire extremity swollen, or just the calf and foot?). Swelling associated with acute DVT is frequently unilateral. The entire extremity may be swollen in patients with iliofemoral venous thrombosis, while femoropopliteal venous obstruction frequently results in swelling of the calf or distal extremity. The left leg is more commonly affected.<sup>24</sup> If there is unilateral swelling, it should also be determined if this results in a measurable discrepancy in the size of the leg relative to the contralateral extremity. In patients with unilateral swelling resulting in a difference in leg circumference of more than 3 cm, the potential for a deep venous thrombotic process is high.<sup>25</sup> In contrast, absence of a significant change in limb circumference is associated with a very low likelihood of a DVT. Physical examination should also include the joints as well as other skin changes, as joint pain and localized cellulitis are rarely associated with DVT.

Homans sign describes the association between calf vein thrombus and calf pain with passive dorsiflexion of the foot. Other clinical findings that have been associated with acute DVT include the Bancroft sign, or tenderness on anteroposterior but not lateral compression of the calf, and the Lowenberg sign, which is calf pain associated with inflation of a blood pressure cuff about the calf. Unfortunately these “signs” persist in the literature and within medical documentation despite the fact that none of them are diagnostic of DVT.<sup>12</sup>

### Phlegmasia

In the patient with DVT, the extremity may appear discolored. Phlegmasia alba dolens, or “milk leg of pregnancy,” describes a pale, white extremity (Fig. 20.7), which was frequently seen in the postpartum period. Homans<sup>26,27</sup> attributed the finding to an underlying iliofemoral venous thrombosis. Collateral veins were noted over the upper thigh and abdomen. The swelling was frequently associated with fever as well as pain in the calf, popliteal fossa, or groin. The absence of bluish discoloration was attributed to the rapid development of collateral venous flow. Phlegmasia cerulea dolens is associated with extensive proximal venous obstruction and minimal collateralization. The leg is massively swollen and cyanotic in appearance. The affected extremity begins to sequester fluid in the interstitium, and massive swelling ensues. The examiner should perform a bedside Doppler examination to confirm the presence of multiphasic flow in the tibial arteries; the swelling and edema are often so significant that palpation of pulses is rendered useless. As interstitial fluid accumulates within the muscular compartments, findings consistent with compartment syndrome may be present. A prompt diagnosis of phlegmasia cerulea dolens is critical, as the limb is salvageable with appropriate and aggressive therapy; however, progression to venous gangrene and limb loss in this setting can occur despite maximal medical and surgical therapy.

### Superficial Thrombophlebitis

Thrombosis of the superficial veins results in localized inflammation surrounding the affected vein or veins. As opposed to



**Figure 20.7** Clinical example of phlegmasia alba dolens. (From Rutherford 9th edition, Fig. 153.1A, p. 2011).

deep venous obstruction, venous hemodynamics in the deep veins of the lower extremity are not usually affected by a superficial thrombophlebitis. Patients who present with superficial thrombophlebitis of the great saphenous vein, however, do have an approximate 10% risk of progression to DVT primarily involving the common femoral vein of the affected extremity.<sup>28</sup> Similar to any thrombotic process, risk factors for superficial thrombophlebitis include advancing age, obesity, history of DVT, previous history of superficial thrombophlebitis, and recent cannulation of the affected vein. The latter is most common in the upper extremity, where it can be associated with a fever of unknown origin.

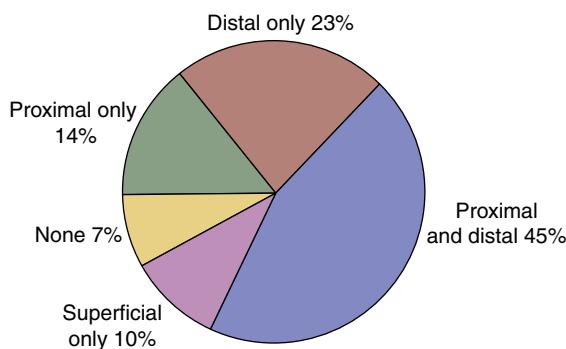
### Physical Examination

Patients presenting with superficial thrombophlebitis will generally complain of pain, tenderness, and warmth over the involved vein with a cord palpable subjacent to the area of the pain. Additionally, erythema with proximal streaking is not uncommon. The presence of erythema is often misconstrued as a cellulitis, and it is not uncommon for patients to be placed on antibiotics. If conservative therapy does not produce expected resolution of the thrombotic process in patients with extensive involvement of the extremity along the length of a named superficial vein, consideration should be given to anti-coagulation (see Ch. 151, Superficial Thrombophlebitis and Its Management).

### Post-Thrombotic (Post-Phlebitic) Syndrome

#### *Pathophysiology and Clinical History*

Chronic venous insufficiency (CVI) is generally thought to be secondary to venous valvular dysfunction following an episode of DVT, resulting from fixed apposition of the venous valves to the wall of the vein with subsequent incompetence after recanalization. Unfortunately, although many patients have recanalization of their previously occluded veins, almost half of such



**Figure 20.8** Distribution of venous valvular incompetence in limbs with stasis ulcers and pigmentation. (From Rutherford, 6th edition, Fig. 9.51, p. 113.)

patients have residual partial thrombosis, which also contributes to symptoms.<sup>29</sup> The combination of venous obstruction and valvular incompetence can be associated with worsening symptoms with physical activity to the point of effort discomfort, often referred to as “venous claudication.” Thrombotic obstruction of the venous outflow and venous insufficiency can also result in ambulatory venous hypertension and edema. Long-standing ambulatory venous hypertension and swelling can ultimately result in the development of venous stasis ulceration (Fig. 20.8).

Initial presenting symptoms include mild swelling and discomfort at the end of the day relieved by rest and limb elevation. The wearing of compression stockings, in general, will significantly improve the patient’s symptoms at this stage. As the duration and severity of deep venous insufficiency increases, mild symptomatology is replaced by late findings, which include brawny edema, venous eczema, lipodermatosclerosis ( hemosiderin deposition typically in the gaiter distribution), and eventual progression to venous stasis ulceration, commonly occurring at the level of the medial malleolus.

### Physical Examination

Patients presenting with deep venous insufficiency exhibit mild to significant swelling depending on the stage of presentation. Unilateral swelling is more likely to be venous in nature, whereas bilateral swelling is most often associated with central cardiac or hepatic dysfunction. In the late stages, edema should be pitting and is often 3 to 4+ in nature, although the presence of brawny edema and chronic fibrosis may impede pitting at the level of the ankle in the gaiter distribution (Fig. 20.9). The latter term is derived from the gaiters, or spats, which were garments worn over the shoe and the lower leg below the knee. The patient may have associated varicosities, although these are not a requirement and would be secondary to coexisting superficial venous insufficiency. The presence of active or healed ulcerations should be documented, including the size, depth, and location. Classically, ulcers associated with deep venous insufficiency are located primarily over the medial malleolar region, although in long-standing and severe cases these can be multiple and located throughout the gaiter distribution of the lower leg. Determination of ulcer etiology can be complex and should be made in conjunction with pulse assessment and neurologic examination for sensory deficits.



**Figure 20.9** The “gaiter” distribution of stasis dermatitis and leg ulcers. (From Rutherford, 6th edition, Fig. 1.3, p. 1.)

Chronic ulcers can be associated with arterial ischemia, venous stasis, and neuropathy (Table 20.10). A history of arterial insufficiency, including claudication and rest pain, should be sought. Ischemic ulcers and tissue loss represent the severest manifestation of arterial disease. Diabetic patients can present with arterial disease and peripheral neuropathy. Neuropathy can predispose such patients to neurotrophic ulcers over the weight-bearing prominences of the plantar foot. Venous stasis disease can result in characteristic ulcerations, but associated arterial disease can affect healing and influence treatment. The history should be accompanied by a complete physical examination, beginning with observation and inspection of the extremity. All areas of ulceration and tissue loss should be fully characterized with respect to location and size, and the status of all pulses should be documented.

Ischemic ulcers are usually quite painful, and there is likely to be typical ischemic rest pain in the distal forefoot that occurs nocturnally and is relieved by dependency. At first, these ulcers may have irregular edges, but when chronic, they are more likely to be “punched out.” They are commonly located distally over the dorsum of the foot or toes but may occasionally be pretibial. The ulcer base usually consists of poorly developed grayish granulation tissue. The surrounding skin may be pale or mottled, and signs of chronic ischemia are invariably present. Notably, the usual signs of inflammation one would expect surrounding such a skin lesion are absent, for it is the lack of adequate circulation to provide the necessary inflammatory response for healing that underlies ischemic ulcers.

Neurotrophic ulcers, however, are completely painless but bleed with manipulation. They are deep and indolent and are often surrounded by both acute and chronic inflammatory reaction and callus. Their location is typically over pressure points or calluses. The patient usually has long-standing diabetes with neuropathy characterized by patchy hypoesthesia and diminution of positional sense, two-point discrimination, and vibratory perception.

The so-called venous stasis ulcer, secondary to ambulatory venous hypertension, is located within the gaiter area, most

**TABLE 20.10** Differential Diagnosis of Common Ulcers

Type	Usual Location	Pain	Bleeding with Manipulation	Lesion Characteristics	Surrounding Inflammation	Associated Findings
Ischemic ulcer	Distal, on the dorsum of the foot or toes	Severe, particularly at night; relieved by dependency	Little or none	Irregular edge; poor granulation tissue	Absent	Trophic changes of chronic ischemia; absence of pulses
Neurotrophic ulcer	Under calluses or pressure points (e.g., plantar aspect of the first or fifth metatarsophalangeal joint)	None	May be brisk	Punched out, with a deep sinus	Present	Demonstrable neuropathy
Venous stasis ulcer	Lower third of the leg (gaiter area)	Mild; relieved by elevation	Venous ooze	Shallow, irregular shape; granulating base; rounded edges	Present	Lipodermatofibrosis, pigmentation

From Rutherford 7th edition, Table 13.5, p. 214.

commonly near the medial malleolus. It is usually larger than the other types of ulcers and irregular in outline but also shallower and with a moist granulating base. The ulcer is almost invariably surrounded by a zone containing some of the hallmarks of chronic venous insufficiency – pigmentation and inflammation (“stasis dermatitis”), lipodermatofibrosis, and cutaneous atrophy. Ulcerations of long duration should undergo biopsy to rule out malignancy.

### May–Thurner Syndrome

May–Thurner syndrome is a specific anatomic diagnosis arising from stenosis or obstruction of the left common iliac vein as it crosses under the right common iliac artery with an associated band or web found at the site of obstruction.<sup>30</sup> Patients usually present with unilateral swelling of the left lower extremity that is aggravated by exercise and activity. “Venous claudication” described as an intense pain, or a bursting sensation, is induced by exercise and relieved by rest and elevation of the limb. This contrasts with arterial claudication, where the cessation of activity and standing rest result in relief.

### Physical Examination

Symptoms classically occur in young women, beyond puberty, who present with either provoked or unprovoked DVT of the left leg. Without treatment, limb swelling and venous claudication may develop. Alternatively, and less commonly, unilateral swelling of the left leg, varicose veins, and venous ulcers may occur. However, many patients with May–Thurner anatomy remain entirely asymptomatic throughout their adult lives despite imaging that suggests venous compression.<sup>30,31</sup>

### Superficial Venous Insufficiency

#### Pathophysiology and Clinical History

Superficial venous insufficiency is classically thought to be caused by incompetent valves at the saphenofemoral and

saphenopopliteal junctions, with subsequent loss of valvular function along the length of the great and small saphenous veins, respectively. Findings of superficial venous insufficiency include telangiectasias, reticular varicosities, and large ropey varicose veins. The large varicose veins can generally be traced back to the great or small saphenous veins. Most patients with varicose veins are women with a significant hereditary component as well as specific risk factors including multiple pregnancies, with general worsening of the varicosities with each successive pregnancy. Patients with varicose veins usually do not complain of severe pain; typically, the discomfort is described as burning or throbbing in character and is localized to the varicosities. Swelling of the calf, and rarely the proximal foot, can often be associated with varicosities. The symptoms associated with varicose veins are relieved with elevation of the extremity, and patients frequently note an absence of symptoms in the morning.<sup>32</sup> They also observe that symptoms increase during the course of the day, particularly if the patients are ambulatory and active with episodes of standing and sitting for long periods of time. Compression stockings are usually effective and significantly improve the symptoms in patients with superficial venous insufficiency.

### Physical Examination

The patient with varicose veins should be examined in the standing position. The location of all varicosities should be noted. The presence of ankle flare or corona phlebectatica should be noted. Additional venous abnormalities may include telangiectasias, which are dilated intradermal venules about 1 mm in size. Reticular veins are nonpalpable subdermal veins measuring 1 to 3 mm in size.

Varicosities along the medial leg are generally related to the great saphenous vein or its perforating branches; varicosities over the posterior calf are in the distribution of the small saphenous vein, which begins on the lateral aspect of the foot and ascends along the posterior midline of the calf. Venous reflux in the great saphenous vein may be associated

with incompetence at the saphenofemoral junction or related to incompetent deep and perforating veins. The great saphenous vein can communicate with the Dodd, Boyd, Cockett, Sherman, and Hunterian perforating veins (see Fig. 20.3). Hunterian perforator incompetence can be associated with varicosities in the middle third of the thigh. The Dodd perforator is located along the medial and distal third of the thigh; Boyd perforators are along the medial aspect of the knee; the Cockett and Sherman perforators are located at the ankle. Duplex ultrasound is necessary to further localize perforators.

In moderate to morbidly obese patients, varicosities may not be visible but may be palpable. Physical examination should include an assessment of varicosities throughout the upper and lower extremities via observation and palpation. Prominent veins, especially in the upper extremity, can signal the presence of normal but prominent veins in the lower extremities.

The Aberdeen Varicose Vein Questionnaire (see Table 20.7) is a patient-reported disease-specific quality-of-life outcome measure used with patients with varicose veins. It includes 12 questions about pain, skin changes, the use of support stockings, appearance and impact, and has been used to compare outcomes in clinical trials of varicose vein therapy.<sup>33,34</sup>

The Trendelenburg and Perthes tests are described here for completeness, however, they are used infrequently in clinical practice, given the ubiquitous use of duplex ultrasound examination of patients with superficial venous insufficiency; this renders the test useful in only very selected circumstances. During the Trendelenburg test, the patient is initially supine, with the extremity elevated. Manual compression or a tourniquet is used to occlude the proximal great saphenous vein. The patient then stands upright. In the absence of significant deep venous insufficiency and perforator incompetence, the superficial varicosities will fill slowly over approximately 20 seconds. On repeating the maneuver, release of compression when the patient first stands will result in rapid filling of varicosities in the presence of significant proximal incompetence. With the Perthes test, a tourniquet is used to occlude the proximal superficial veins. As the patient ambulates, the varicosities enlarge if there are incompetent perforating veins. Use of a handheld Doppler in conjunction with these tests markedly improves the diagnostic accuracy.<sup>35</sup>

## Klippel–Trenaunay Syndrome

### *Pathophysiology and Clinical History*

Klippel–Trenaunay syndrome comprises a constellation of findings including varicose veins, a port-wine stain, and associated hypertrophy of the bone and soft tissue, resulting in limb-length discrepancy. With associated arteriovenous malformations, the condition is more correctly termed Parkes Weber syndrome or Klippel–Trenaunay–Weber syndrome.

Most patients present with unilateral limb involvement, with the lower extremity being the most frequent site. A port-wine stain is the most common finding, followed by the presence of varicosities and then by limb hypertrophy. The varicose veins and port-wine stain are invariably congenital and present

at birth. Venous involvement can be associated with pain or venous ulcerations.<sup>36</sup>

### *Physical Examination*

The patient's extremity should be examined for the presence or absence of other defining arteriovenous malformations or limb abnormalities. In isolated Klippel–Trenaunay syndrome, the port-wine stain is most frequently located on the affected limb. The varicosities associated with the condition are classically described as arising from the foot or the lower leg, extending proximally into the thigh or gluteal area. The varicose veins can be prominent or may only present with ambulation. In some cases, varicosities may not be present until the onset of puberty. Veins in the saphenous vein distribution are frequently spared. Prior to treating the varicosities, it is essential to ensure the presence of a patent deep venous system, as these patients can often have atretic deep veins.

## Venous Aneurysms

### *Pathophysiology and Clinical History*

Venous aneurysms, while not common, have been reported to occur in the superficial and deep veins of the upper and lower extremities.<sup>37–39</sup> By definition, a venous aneurysm cannot be associated with an arteriovenous malformation or pseudoaneurysm, and must be an isolated, solitary dilatation in line with a vein. There appears to be an equal incidence in men and women and there is no age predilection; studies have shown a correlation with saphenous vein reflux. The presumed rarity may be related to the fact that superficial aneurysms are frequently asymptomatic, unreported, or misdiagnosed as a soft tissue mass. Patients with aneurysms of the superficial veins can present with swelling, with or without associated discomfort. Aneurysms of the deep veins commonly present following thrombosis, frequently of the popliteal vein, or pulmonary embolus.<sup>37</sup> Pathologically venous aneurysms are associated with a reduction in smooth muscle cells or an increase in fibrous connective tissue.<sup>38</sup> The etiology may be congenital, secondary to trauma, or associated varicose veins. There has been a reported association with Klippel–Trenaunay and Servelle–Martorell syndromes.<sup>39</sup>

### *Physical Examination*

On examination, superficial venous aneurysms may involve the upper or lower extremities. Examination is best with the patient in the standing position, as this helps to accentuate the aneurysmal dilatation. Care should be taken in the examination of groin masses, as a saphenous vein aneurysm can be mistaken for a femoral or inguinal hernia. Pain can be associated with thrombosis of the aneurysm. Aneurysms associated with the saphenous vein can be classified into four types; those involving the proximal thigh (type 1), those involving the distal thigh (type 3), and aneurysms occurring in both the proximal and distal thigh (type 2); type 4 aneurysms involve the small saphenous vein.<sup>39</sup> Aneurysms involving the deep veins of the lower extremity frequently present with findings consistent with a DVT. Diagnosis generally occurs following a duplex ultrasound evaluation.

**TABLE 20.11** Etiologic Classification of Lymphedema

I. Primary Lymphedema	
A.	Congenital (onset before 1 year of age)
1.	Nonfamilial
2.	Familial (Milroy disease)
B.	Praecox (onset at 1–35 years of age)
1.	Nonfamilial
2.	Familial (Meige disease)
C.	Tarda (onset after 35 years of age)
II. Secondary Lymphedema	
A.	Filarisis
B.	Lymph node excision / radiation
C.	Tumor invasion
D.	Infection
E.	Trauma
F.	Other

From Rutherford, 6th edition, Table 167.1, p. 2397.

## Lymphedema

### Overview/Pathophysiology

Lymphedema (see Ch. 167 Lymphedema: Evaluation and Decision Making) results from obstruction of the lymphatics, with resultant accumulation of protein and fluid in the interstitial tissues of the extremity. Lymphedema may be classified based on underlying etiology, genetic predisposition, morphology, and age of onset. Clinically, lymphedema is grossly classified as primary/intrinsic or secondary to other contributing factors (Table 20.11).<sup>40–42</sup> Primary etiologies are characterized by the age of onset; lymphedema may present as a congenital condition at birth, at puberty through adolescence, or later in life. Genetically, lymphedema may be familial or sporadic. Morphologically, lymphedema is the result of lymphatic aplasia, hypoplasia, hyperplasia, or less commonly incompetence of the lymphatic system. Genetic predisposition and lymphatic morphology are most useful in predicting clinical severity and guiding potential therapies. Risk factors for lymphedema can include malignancy, age, obesity, and autoimmune conditions. Staging of lymphedema may be based on clinical stage or anthropometric measurement. The International Society of Lymphology<sup>43</sup> and the National Cancer Institute Common Terminology Criteria for Adverse Events<sup>44</sup> use clinical findings to identify stage or grade. The American Physical Therapy Association<sup>45</sup> reviewed clinical practice guidelines for the assessment of upper extremity lymphedema secondary to cancer, suggesting the use of volume differences between the involved and uninvolved extremity and the use of bioimpedance analysis. Their report also assesses the value of several self-report questionnaires.

### Primary Lymphedema

Primary lymphedema can present at birth as a congenital condition and is more common in men, with most patients presenting with involvement of the lower extremity (>80%). Milroy disease is a familial variant.<sup>46</sup> It is more common in women and is associated with a mutation of the *VEGFR-3* or *FLT4* genes. It is frequently bilateral. Men can have an associated hydrocele,

**TABLE 20.12** Clinical Staging of Chronic Lymphedema

Grade I	Early pitting prevalent that reduces with elevation No fibrotic skin thickening
Grade II	Skin thickened and fibrotic pitting only to deep prolonged pressure Often no pitting No reduction with elevation overnight
Grade III	Skin fibrotic and sclerotic in subcutaneous tissues Often secondary hyperkeratosis Verrucal development These changes are permanent

and men and women can have papillomas. Primary lymphedema can be associated with other syndromes including Turner syndrome, Noonan syndrome, Klinefelter syndrome, hemangiomas, trisomy 13, trisomy 18, neurofibromatosis type 1, yellow nail syndrome, congenital nail absence, distichiasis, lymphedema syndrome, and xanthomatosis.

Lymphedema praecox (or its familial variant, Meige disease) is the most common form of lymphedema, primarily affecting women between the ages of 10 and 35. It is commonly associated with puberty. It accounts for over 80% of all patients with lymphedema. Lymphedema tarda generally presents in patients over 35 years of age and occurs more commonly in women.<sup>47</sup>

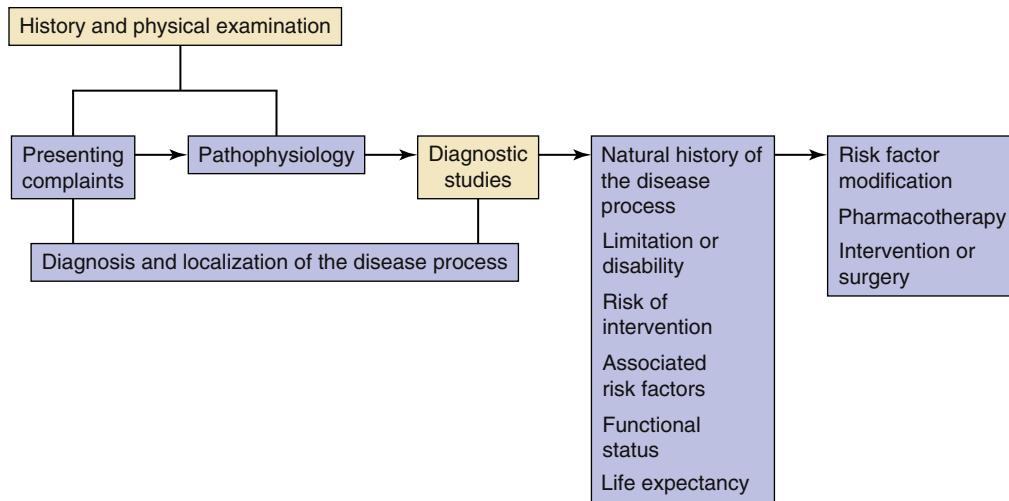
### Secondary Lymphedema

Secondary lymphedema is more common than primary lymphedema and results from any process leading to lymphatic injury, such as infection and filariasis. Patients who present with a sudden onset lymphedema later in life should be questioned about international travel.<sup>48</sup> In developed countries the most common cause of secondary lymphedema is direct injury or surgical dissection of regional lymph nodes and also trauma, cancer (tumor, surgery, or radiation), and infection.<sup>49</sup>

### Physical Examination

Lymphedema most commonly involves the lower extremities. In the upper extremity, it can be associated with prior mastectomy and axillary lymph node dissection. It is unilateral, and elevation of the extremity generally does not result in resolution of the swelling.<sup>50</sup> In the lower extremity, swelling generally begins distally, involving the area about the ankle; it rarely spares the toes and foot, which differentiates lymphedema from other conditions. At onset, the swelling begins as mild pitting edema, slowly increasing in extent, that is relatively painless in character. The edema may progress to involve the proximal extremity, including the genitalia and trunk. The Stemmer sign describes the inability to pinch and lift the dorsal skin of the foot between the first and second toes; if the skin fold cannot be lifted, the test is indicative of lymphedema. Additionally, with lymphedema, the toes can become squared, suggesting the appearance of “boxcars.”<sup>51</sup> With progression of the lymphedema, fibrosis develops in the subcutaneous tissues, with subsequent ulcerations, fissures, and lymphorrhea. Not infrequently, patients may present with inflammation secondary to lymphangitis and red streaks in the distribution of the lymphatic channels (Table 20.12).

## CHAPTER ALGORITHM



This algorithm illustrates the stepwise evaluation and management of patients presenting with arterial, venous, or lymphatic disease. The diagnosis and localization of the disease process involves the history and physical examination and any indicated diagnostic studies. The history and physical examination identify the presenting findings and provide a bridge to potential pathology and pathophysiology. Therapy is dependent upon the natural history of the disease process and its impact on the patient's quality of life as well as the patient's associated risk factors and functional status. (From Rutherford, 7th edition, Fig. 13.1, p. 204.)

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A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com).

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# Vascular Laboratory: Arterial Physiologic Assessment

MATTHEW H. RECHT and PATRICK E. MUCK

Based on a previous edition chapter by Gale L. Tang and Ted R. Kohler

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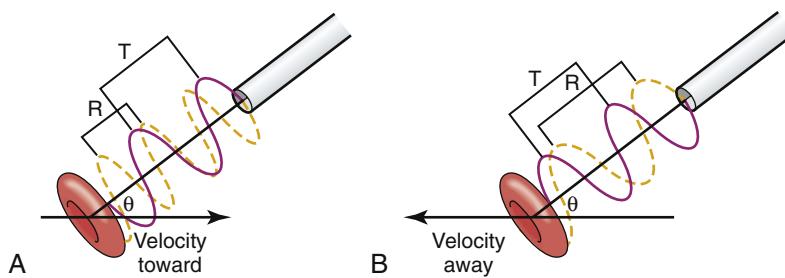
Arterial physiologic testing adds a degree of objectivity to the subjective clinical evaluation of peripheral arterial disease (PAD). The advances in direct physiologic testing of specific arterial sites by duplex scanning and noninvasive imaging evaluation provide the approximate localization of extent of disease and therefore indirect physiologic testing is now less critical (see Chapter 22, Vascular Laboratory: Arterial Duplex Scanning). However, physiologic testing is helpful when the diagnosis is uncertain, such as in patients with possible neurogenic claudication. These tests are also useful in determining the extent to which arterial disease limits walking in patients who have concomitant orthopedic or neurologic problems contributing to their disability. Noninvasive testing can be used to detect PAD in otherwise asymptomatic patients, and this can be valuable since PAD is an independent risk factor for cardiac events and the early diagnosis of PAD can initiate risk factor modification.<sup>1–3</sup> In patients with advanced disease, physiologic testing helps to determine the ability of ischemic ulcers to heal or provides guidance for the optimal level of amputation. This chapter reviews the theory, methods, interpretation, and applications of the various indirect physiologic arterial tests available in the vascular laboratory.

## DOPPLER ULTRASONOGRAPHY

The development of Doppler ultrasound to detect blood flow and analyze velocity waveforms revolutionized the ability to detect and quantitate peripheral vascular disease noninvasively.<sup>4</sup> This chapter discusses the use of basic continuous wave Doppler and waveform analysis.

### Principles of Doppler Ultrasound

The handheld continuous wave “pocket Doppler” devices typically have a transmitting frequency between 5 and 10 MHz, suitable for more superficial arteries due to the limited penetration depth of ultrasound waves at this frequency. The tip of the probe has a transmitting piezoelectric crystal that converts electrical energy into ultrasound waves, as well as a receiving piezoelectric crystal that detects reflected ultrasound waves. The probe converts detected frequency shift and sends it to the speakers for an audible signal. A fluid interface, generally an aqueous gel, is required between the probe and the skin to allow penetration of ultrasound waves into the tissue without significant loss of energy from impedance mismatch (difference



**Figure 21.1** The Doppler device compares the frequency of backscattered sound from moving red blood cells with the transmitting frequency to determine the frequency shift, which is proportional to the speed of the flowing blood, the transmitting frequency, and the cosine of the Doppler angle,  $\theta$ . The drawing shows a Doppler probe transmitting ultrasound at a wavelength  $T$  to a red blood cell moving in a direction indicated by an arrow. The red cell is moving toward the probe in (A) and away from the probe in (B). The angle between the ultrasound beam and the direction of red cell velocity is given by  $\theta$ . The frequency of the ultrasound that is transmitted is the same in both cases (red line). The ultrasound signal that is received (yellow line) has a shorter wavelength ( $R$ ) and thus a higher frequency in (A) and a longer wavelength and lower frequency in (B).

in density causing significant reflection of ultrasound waves, thus preventing further tissue penetration). Moving red blood cells act as reflectors that backscatter ultrasound waves. The frequency of the reflected ultrasound wave is shifted from the transmitted frequency in direct proportion to the velocity of the blood flow due to the Doppler effect (Fig. 21.1). The magnitude of the frequency shift ( $\Delta f$ ) is given by the following Doppler equation:

$$\Delta f = \frac{2V f_0 \cos\theta}{C}$$

where  $V$  is blood velocity in centimeters per second,  $f_0$  is the transmitted frequency,  $\theta$  is the angle between the velocity vector and the path of the ultrasound beam (known as the Doppler angle), and  $C$  is the velocity of sound through blood ( $1.54 \times 10^5$  cm/s). This equation can be rearranged to solve for  $V$  when the Doppler angle is known, or it can be estimated, as it is in duplex scanning.

### Aural Interpretation of the Doppler Waveform

The velocity of blood flow is proportional to the frequency shift, which is heard as a change in pitch of the audio signal. Loudness (amplitude) is proportional to the volume of red blood cells moving through the Doppler signal path. Turbulence causes nonuniform velocities and imparts a harsh quality to the audible Doppler signal. An experienced listener can identify increased pitch, which corresponds to luminal narrowing causing increased velocity of flow. One can also assess the contour of the velocity waveform. Normal peripheral arteries at rest have a triphasic or biphasic quality with a brisk upstroke of forward flow in systole, a brief reverse flow component in diastole caused by the reflection of the flow wave from the high resistance periphery, and finally, in most, but not all peripheral arteries, a small forward component in late diastole (Fig. 21.2A and B). When the peripheral vascular resistance is low, either due to the arterial bed downstream such as the kidneys, brain, or liver, or after exercise, hyperemia, or intraarterial administration of vasodilating drugs, the velocity waveform loses the

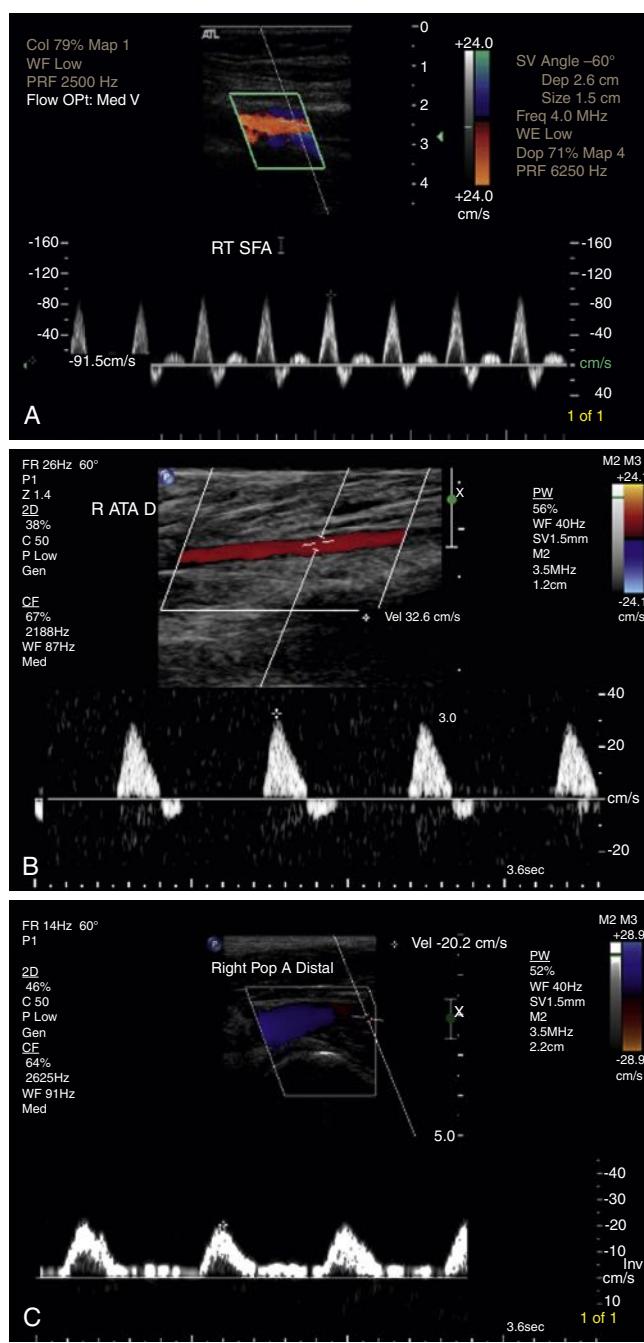
reverse flow component and becomes monophasic with forward flow throughout the entire cardiac cycle.

Arterial obstruction causes dampening of the waveform, which becomes monophasic (Fig. 21.2C). The low-amplitude, monophasic Doppler signals that result from extensive occlusive disease may be difficult to distinguish from venous signals. Gentle compression of the foot causes a rush of venous blood from emptying the veins that is easy to appreciate in the Doppler signal. Directional Doppler can also be useful to distinguish arterial from venous signals because it will indicate whether blood is flowing toward or away from the ultrasound probe.

### Qualitative and Quantitative Waveform Analysis

The earliest change at the site of stenosis is widening of the waveform (spectral broadening) in early diastole, when flow is decelerating and least stable. More severe stenosis produces a marked increase in systolic velocity in addition to spectral broadening. Critical stenosis limits flow and pressure and generally occurs when the lumen is narrowed by 50% or more. Waveforms at the site of stenosis are associated with a doubling of peak systolic velocity when compared with the adjacent segments (Fig. 21.3). Downstream from significant stenoses, waveforms become blunted and monophasic with widening as a result of turbulence.

The result is a noisy, high-pitched Doppler signal at the site of stenosis. This signal can be heard for several vessel diameters downstream from the site of stenosis because of transmission of the high-velocity jet over this distance. A few centimeters upstream from the stenosis, the waveform is affected by the high resistance of the stenosis. This results in less forward flow and a large, reflected wave following the lower frequency systolic peak. It is heard as a “to-and-fro” signal pattern. Extremely low flow may not be detectable by handheld Doppler instruments because of inadequate signal generation or cutoff of very low frequencies by the filter that is used to eliminate wall motion artifacts.



**Figure 21.2** Normal and Dampened Velocity Waveforms Obtained with a Duplex Scanner. (A) Normal triphasic velocity waveform. (B) Biphasic velocity waveform. (C) Monophasic velocity waveform.

To overcome the subjective, operator-dependent nature of qualitative waveform analysis, spectrum analyzers can be used. These instruments have a frequency analyzer that uses fast Fourier analysis or similar methods to give a full picture of the entire spectrum of frequencies present in each sampling interval. Frequency shifts are displayed on the vertical axis and time on the horizontal axis. The amplitude of the reflected signal at each frequency is represented by a gray scale (see Fig. 21.2). The intensity of the gray scale is proportional to the number of red blood cells traveling at a particular velocity at each point

in time. These devices, which are used in all duplex scanners, permit identification of features, such as uniformity of flow (narrow band of velocities) or nonuniformity (widening of the velocity waveform, known as spectral broadening). When the angle of insonation is known, the output can be displayed as velocity over time and various parameters can be measured, such as peak and end-diastolic velocity and ratios of various velocity components. Duplex scanners also use pulsed Doppler with time-gated reception of the reflected ultrasound to allow the operator to select the depth at which velocity information is obtained. This permits interrogation of Doppler information within a visualized vessel and thereby more precise categorization of the degree and location of stenosis. In the absence of Duplex scanning, indirect analysis of waveforms obtained at the common femoral artery level such as peak-to-peak pulsatility index (calculated as  $(V_{\max} - V_{\min})/V_{\text{mean}}$  where  $V$  stands for velocity, max for maximum, and min for minimum), Laplace transform, power frequency spectral analysis, pulse wave velocity, and pulse transit time have been used to determine whether significant aortoiliac occlusive disease is present. However, these indirect methods are prone to false-negative interpretations because waveforms can return to a normal contour within only a few vessel diameters downstream from a significant stenosis.<sup>5,6</sup>

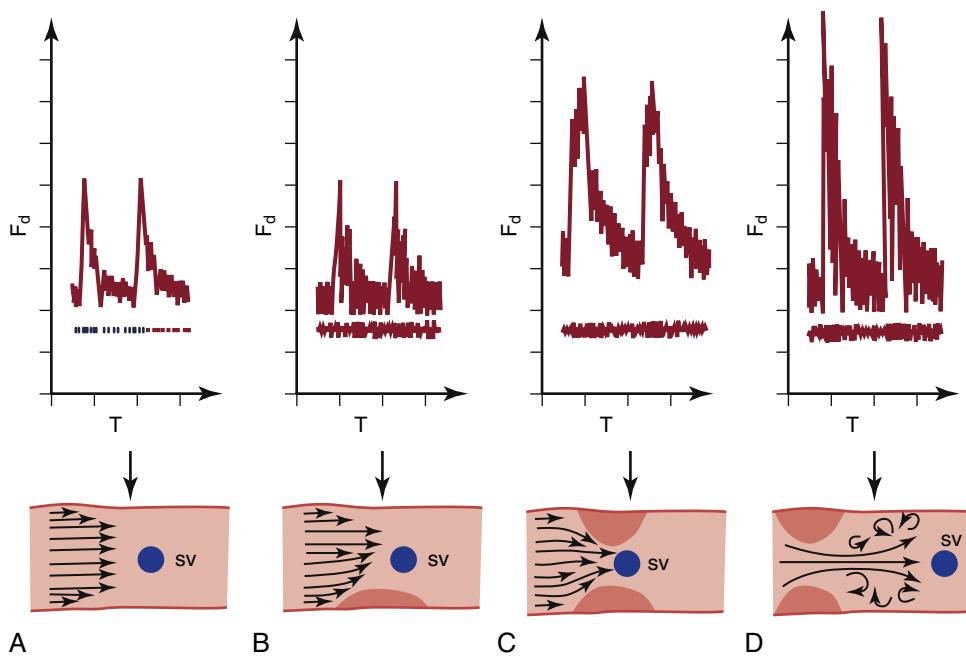
## PRESSURE MEASUREMENTS

Strandness and coworkers developed noninvasive pressure measurement in the 1960s when continuous wave Doppler instruments became available to detect blood flow.<sup>4</sup> Since pressure differentials drive flow, decreased pressure results in decreased flow. In most instances, therefore, pressure is an acceptable surrogate measure for flow and is easier to measure.

The higher-frequency components of the pressure waveform are more sensitive to the dampening effect of stenoses, and therefore decreases in systolic pressure are more sensitive than changes in mean or diastolic pressure for detecting stenosis. The reduction in pressure is caused by viscous losses from flow through narrow channels and by kinetic energy losses secondary to turbulence (which is the dominant source of loss in all but the smallest arteries). Turbulence occurs when kinetic forces are much greater than the viscous forces that produce ordered, laminar flow. The relationship between these forces is estimated by the Reynold number ( $Re$ ):

$$Re = Vd/v$$

where  $V$  is velocity in centimeters per second,  $d$  is diameter of the vessel, and  $v$  is viscosity (which varies with velocity; in other words, blood is a non-Newtonian fluid). As flow increases, velocity increases, and flow becomes less stable as both viscous and kinetic losses increase. Greater than Reynold numbers of approximately 2500, turbulence develops (at least in straight tubes with nonpulsatile flow, conditions that are not met in the normal human vasculature) and energy is lost (as imperceptible heat generation). Thus resting flow and velocity may not be associated with a reduction in pressure. However,



**Figure 21.3** Changes in the Velocity Waveform Caused by Arterial Stenosis. (A) Normal waveform with relatively low and uniform velocity (frequency shift). (B) Mild stenosis causes disturbed flow in diastole (broadened waveform) and little increase in velocity. (C) Significant narrowing ( $>50\%$ ) causes at least a doubling of the peak systolic velocity. (D) Beyond a significant narrowing, post-stenotic turbulence causes marked widening of the waveform.  $F_d$ , frequency shift; SV, sample volume; T, time. (Compliments of Jean Primozich.)

a pressure gradient may develop when flow increases, resulting in increased turbulence.

A mild stenosis that does not cause a drop in pressure at rest may become evident when flow is increased. A peak systolic pressure drop across an arterial segment of 10 mm Hg at rest or 15 mm Hg after hyperemia induced by exercise, ischemia, or the administration of vasodilators indicates increased resistance in this segment sufficient to reduce flow by a clinically meaningful amount. Conversely, significant proximal lesions (e.g., in the aortoiliac system) may not be evident even after vasodilation if the outflow vessels (superficial and profunda femoral arteries) are so diseased that outflow is severely restricted. If there is minimal flow, there is no pressure drop across a vessel no matter how stenotic.

## Ankle–Brachial Index Measurement

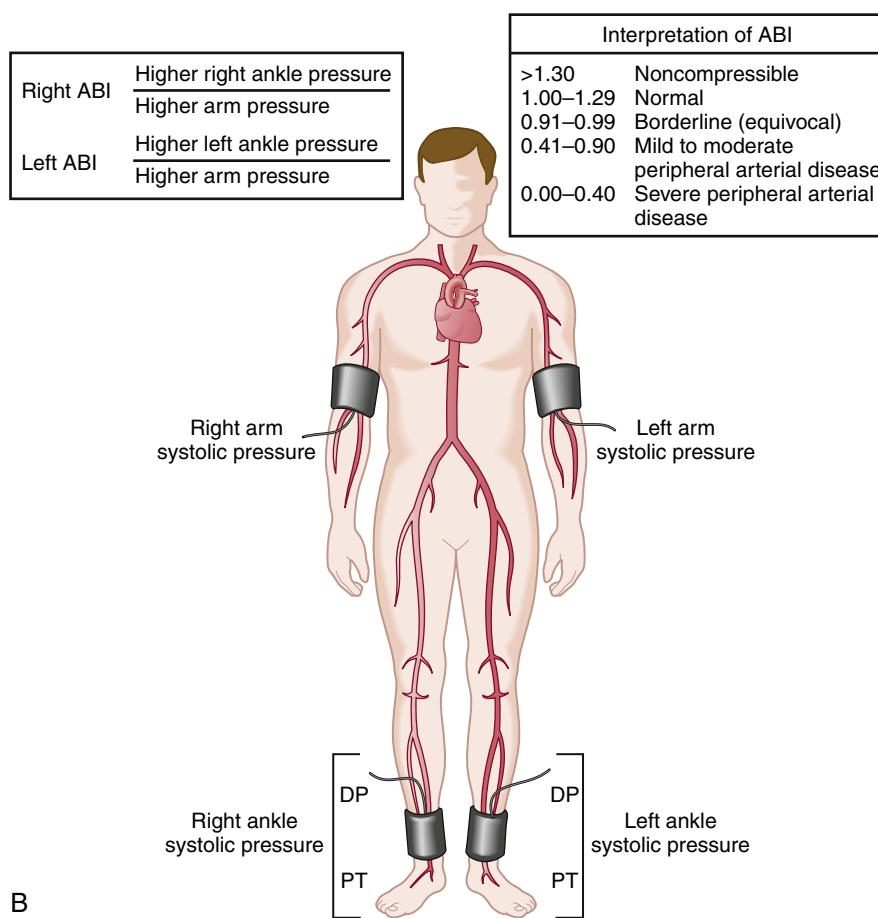
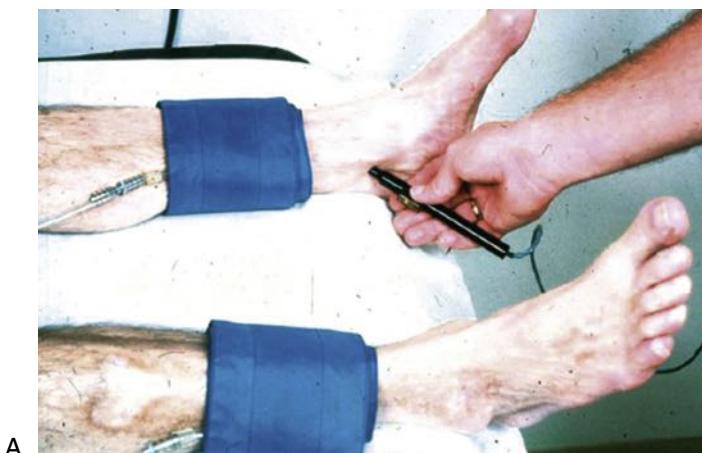
### Basic Technique

The simplest noninvasive method for documenting the presence of lower extremity arterial occlusive disease is the ankle–brachial index (ABI).<sup>7</sup> The cuff is placed as low as possible on the leg above the ankle, inflated above systolic pressure, and then slowly deflated while the Doppler probe is held over the posterior tibial artery, just behind the medial malleolus (Fig. 21.4A), or the dorsalis pedis artery, slightly lateral to the extensor hallucis longus tendon approximately a centimeter distal to the ankle joint. The ankle pressure is recorded as the highest pressure at which the Doppler signal returns. If no signal can be obtained over these arteries, the examiner should check for the terminal branch of the peroneal artery (the lateral tarsal

artery), which is just anterior and medial to the lateral malleolus. However, pressure in this artery may not be as good a measure of pedal flow as in the other two tibial arteries because it is often not in continuity with the pedal arch.

The brachial pressure, measured with a manual blood pressure cuff and continuous wave Doppler at the distal brachial or radial artery, is used as the denominator for the ABI and serves as a surrogate for central aortic pressure, which cannot be measured noninvasively. As upper extremity occlusive disease may lower brachial pressure, the higher of the two arm measurements should be used. Bilateral upper extremity occlusive disease renders the ABI nondiagnostic. The ABI for each lower extremity is the highest of the detectable ankle pressures divided by the higher of the two brachial pressures (see Fig. 21.4B). The ABI is less variable than ankle pressure, with a standard deviation of approximately 0.07, so a measurement greater than two standard deviations is considered significant. Normalizing to the brachial pressure accounts for the normal variation in central pressure and allows a better appreciation of the extent of arterial occlusive disease in the presence of systemic hypotension or hypertension.

The pressure waveform changes as it moves distally through the vasculature (Fig. 21.5). Peak systolic pressure is accentuated by the additive effect of reflected pressure waves from the periphery. In addition, the lower extremity vasculature remodels in reaction to increased intraluminal pressure from gravity and upright posture to have increased wall thickening and unchanged inner radius, leading to increased arterial stiffness.<sup>8</sup> Thus, although mean pressure decreases as the pressure wave travels distally, peak systolic pressure increases. As a result,

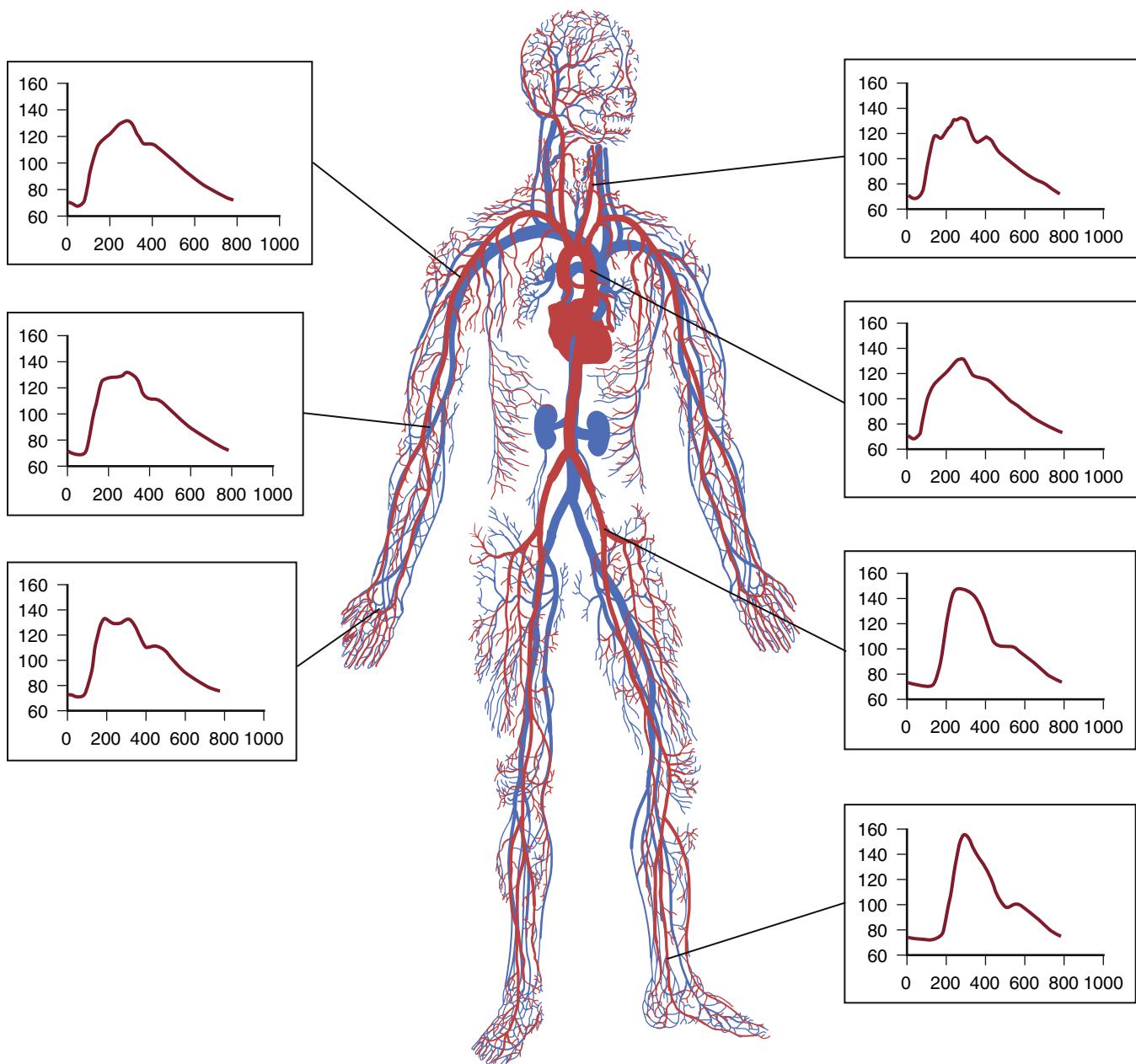


**Figure 21.4** (A) Method for measurement of ankle pressure. The cuff is placed just above the ankle, and pressure is measured over the dorsalis pedis and posterior tibial arteries. The higher of the two is used to estimate perfusion pressure at the ankle. (B) Method for measurement of the ankle-brachial index (ABI). The higher of the two brachial pressures and the higher of the two ankle pressures are used for calculation of the index. The patient should be supine and resting for at least 5 minutes before the measurements are made. *DP*, dorsalis pedis; *PT*, posterior tibial. (From Hiatt WR. Medical treatment of peripheral arterial disease and claudication. *N Engl J Med*. 2001;344:1608–1621.)

ankle systolic pressure is normally approximately 10% higher than brachial pressure (ABI of 1.1). Significant PAD decreases this ratio. Because of the known variance of this test, ABIs in the range of 0.9 to 1.29 are considered normal. However, a value of 0.9 to 1 should be considered borderline because these patients have been demonstrated to have increased lower

extremity and cardiovascular risk.<sup>9</sup> As the extent and severity of PAD increases, ABI decreases (Fig. 21.6A).

ABI has been well validated against contrast-enhanced angiography for its ability to detect stenosis of greater than 50%.<sup>8,10,11</sup> The sensitivity of this test depends on the lower limit of normal that is chosen, with higher limits detecting

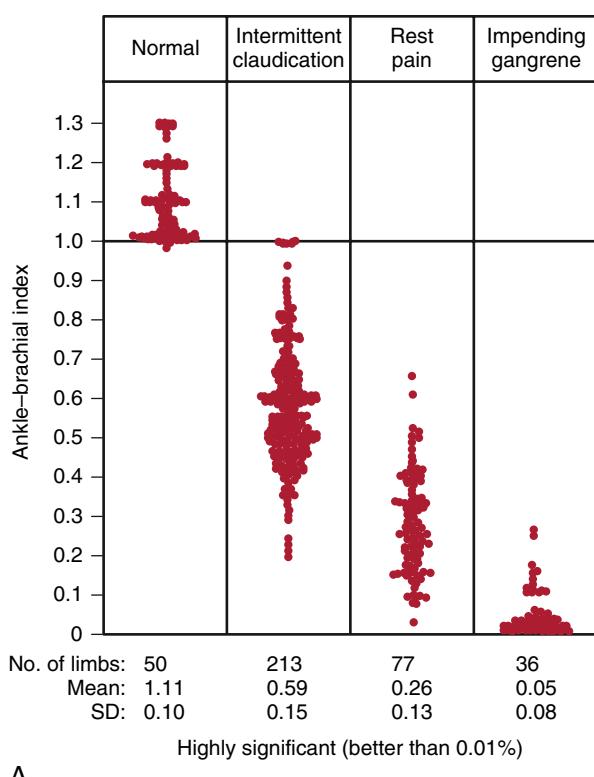


**Figure 21.5** The pressure wave changes as it moves distally through the vasculature. Peak systolic pressure is accentuated, and mean arterial pressure decreases.

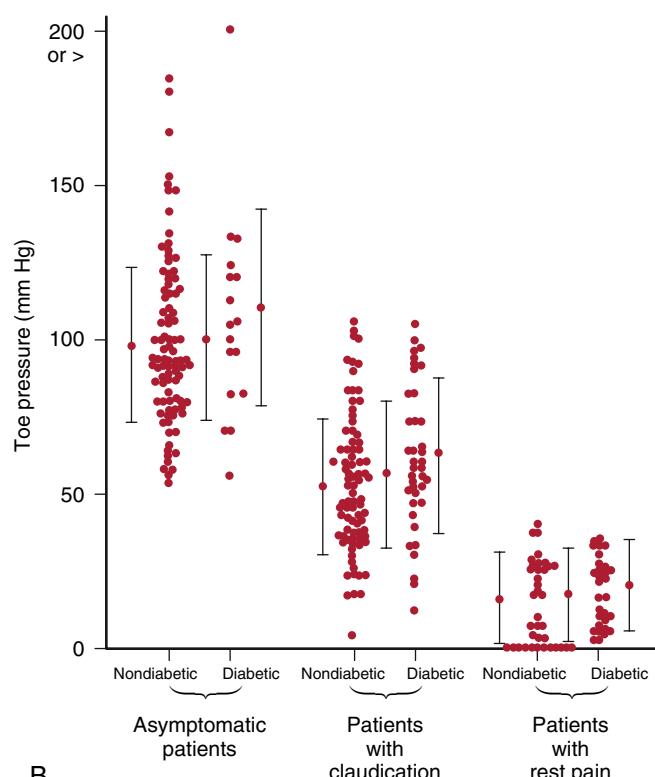
more disease, as well as the population being tested, with lower sensitivity in more elderly populations or with a higher percentage of diabetic or chronic kidney disease patients. Using an average of the two measurements has been found to correlate better with walking distance than using either the lower or higher ankle pressure.<sup>12</sup> In general, the sensitivity of ABI in detecting PAD ranges from 80% to 95% and the specificity from 95% to 100%, with positive and negative predictive values in excess of 90%.<sup>10,13</sup>

The automated blood pressure instruments commonly used in hospitals and clinics to determine arm blood pressures may also be used at the ankle level. The machine detects oscillations of pressure, caused by changes in volume in the extremity as a result of influx of blood with each systolic pulse, in the cuff as it

deflates. Oscillation begins while the cuff is well above systolic pressure and continues until it is well below diastolic pressure. Maximum oscillation occurs at mean arterial pressure. Each manufacturer has its own proprietary algorithm, empirically derived, to determine systolic and diastolic pressure from oscillometry. These algorithms were developed for measurement of arm pressure but can also be used for ankle pressure. Like standard Doppler methods, oscillometry has good concordance for normal ankle pressure, but it overestimates pressure when there is moderate disease and is unable to determine pressure in severe disease due to the significantly diminished pulse pressure. Nevertheless, this method may be useful to screen for PAD in primary care clinics because it is rapid and requires no specialized training or equipment.<sup>8,14</sup>



A



B

**Figure 21.6** (A) Relationship of the ankle–brachial index to functional impairment produced by the occlusive process. *SD*, standard deviation. (B) Toe blood pressure grouped according to symptoms and the presence of diabetes in patients with arterial disease. Mean and *SDs* for the nondiabetic and diabetic subgroups and for the two groups combined are indicated by vertical bars. ([A] Modified from Yao JST. Hemodynamic studies in peripheral arterial disease. *Br J Surg*. 1970;57:761; [B] Modified from Ramsey DE, Manke DA, Sumner DS. Toe blood pressure: a valuable adjunct to ankle pressure measurement for assessing peripheral arterial disease. *J Cardiovasc Surg*. 1983;24:43–48.)

Noninvasive tests can help to make the diagnosis of popliteal entrapment syndrome. A change in ankle plethysmography and ABI with stress maneuvers suggests popliteal entrapment. The limb is examined with the knee extended and the foot in the neutral, forced plantar-flexed, and forced dorsiflexed positions. The test is considered positive if the ABI drops more than 0.5 or there is flattening of the plethysmographic tracing with forced dorsiflexion or plantar flexion<sup>15,16</sup> (see Ch. 144, Nonatherosclerotic Popliteal Artery Diseases).

### Prognostic Value of Ankle–Brachial Index

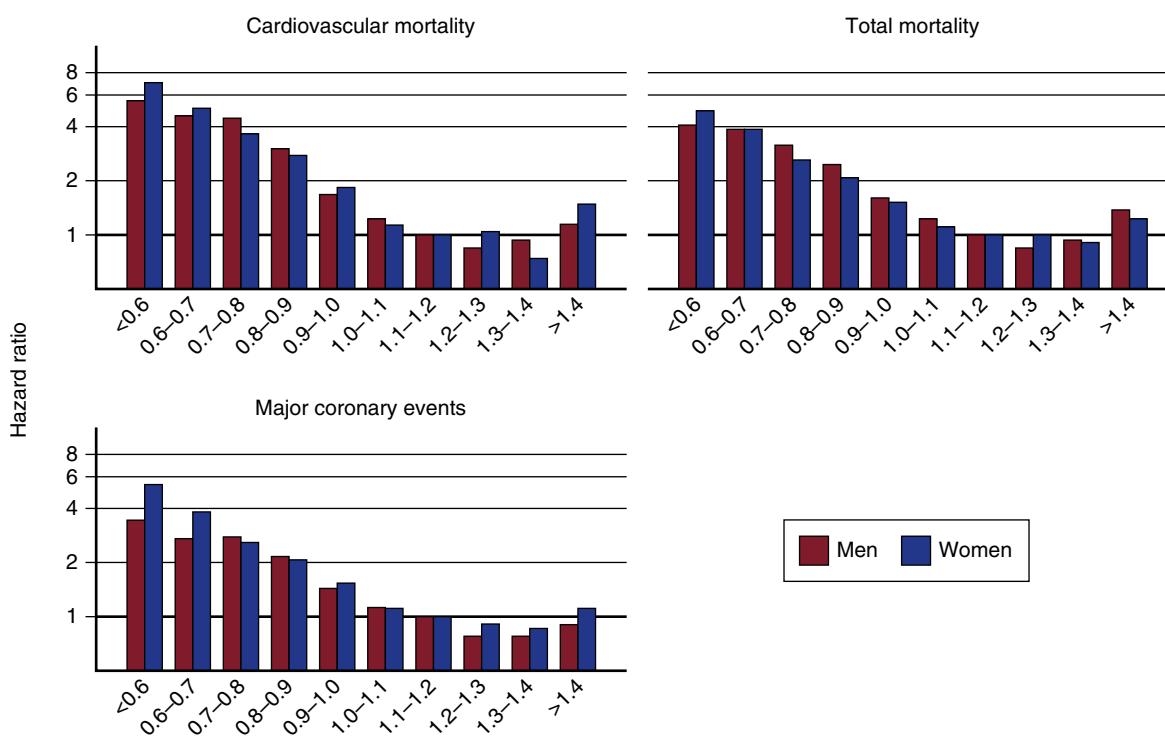
The ABI has predictive value; measurements greater than 0.5 are infrequently associated with progression to critical limb ischemia over the next 6 years.<sup>17</sup> Decreased ABI and the presence of diabetes mellitus were the two factors associated with the development of chronic limb ischemia in a 15-year study of 1244 patients with claudication.<sup>18</sup> An abnormal ABI (either <0.60 or >1.30) has been associated with increased overall mortality, as has decline in ABI over time.<sup>19–22</sup> The ABI is useful as an office screening tool for PAD in asymptomatic patients older than 65 years of age, for whom an ABI <0.90 is associated with an increased mortality and vascular event risk.<sup>23</sup> The American Diabetes Association has recommended similar screening with ABI for diabetic patients older than 50 years of age.<sup>24</sup> Although detection of PAD can identify patients at risk for cardiac events, there are no data demonstrating that

screening leads to prevention of such events. Further, there is no evidence that ABI adds significantly to Framingham Risk Score or other assessments of cardiovascular risk.<sup>25–27</sup> Routine surveillance of ABI is not indicated in untreated patients with PAD unless they develop new or worsening symptoms.<sup>28</sup>

However, cardiovascular mortality, all-cause mortality, and major coronary event rates by gender have not been well defined in population-based studies. There are no known gender-based differences in diagnostic testing of any of the physiologic PAD tests, and all noninvasive studies may be used to document the presence of PAD in women. A trend exists that suggests higher event rates for women than for men for individuals with an ABI <0.90.<sup>29</sup> Women suffer the consequences of PAD at rates at least as high as those observed in men (Fig. 21.7).

### Technical Errors

Although measurement of ABI is straightforward, there are potential inaccuracies. A common mistake made by the uninitiated is to use the left brachial pressure for calculation of the left ABI and the right brachial pressure for the right ABI. Once it is understood that brachial pressure is a surrogate for systemic pressure and that atherosclerosis may lower pressure to an upper extremity, the correct practice of using the higher of the two brachial pressures becomes obvious. Failure to have the patient supine for long enough to allow stabilization of blood pressure, preferably for ≥5 minutes, is the next most common



**Figure 21.7** Hazard ratios (unadjusted) of all-cause mortality, cardiovascular mortality, and major coronary events (coronary death, nonfatal myocardial infarction) in men and women, by ankle–brachial index value. Hazard ratios were calculated with the 1.1 to 1.2 group as the reference (hazard ratio=1.0).

error, particularly when it is difficult to assist nonambulatory patients from a wheelchair onto an examination table. Because hydrostatic pressure is equal to “ $\rho gh$ ” (where  $\rho$  is the density of blood,  $g$  is acceleration as a result of gravity, and  $h$  the height in centimeters of the blood column measured from the right atrium, also known as the phlebostatic level), ankle pressure will be increased by 0.74 times the height in centimeters from the right atrium to the cuff. If the patient is sitting or standing, this distance is on the order of 100 cm; ankle pressure would be elevated by 74 mm Hg above the supine value – a significant difference.

Use of a cuff that is too small will result in poor conduction of pressure to the extremity and falsely elevated readings. Conversely, a cuff that is too wide may cause an underestimation of pressure. The American Heart Association recommends that the bladder length of the cuff be 80% and the width be 40% of the circumference of the extremity (for a length-to-width ratio of 2:1).<sup>30</sup> It may not be possible to measure upper arm pressure accurately in obese patients because the width of a properly sized cuff exceeds the length of the upper part of the arm. In such cases, forearm pressure may be more accurate.

If the artery wall is stiffened by medial calcinosis, as often occurs in diabetics and patients with chronic kidney disease, increased pressure may be required to collapse the wall and stop the flow of blood. An ABI greater than 1.3 should raise suspicion that the wall is stiffened. In the extreme, blood flow is never occluded even at the highest cuff pressure. Stiff arteries may also reopen when cuff pressures are still well above intraluminal pressure, resulting in falsely elevated ankle pressure. There are several ways to suspect that such is the case. First,

the quality of the Doppler waveform, which would be brisk and triphasic in a normal vessel, may be blunted and monophasic because of the occlusive disease (see below). Second, the pulse may not be palpable even though the measured pressure is well above the palpable level. Third, the remainder of the clinical picture, such as ischemic ulceration or a clear history of claudication or pain at rest in a patient with known atherosclerosis, may be strongly suggestive of significant PAD. Fourth, the Doppler signal may diminish if the ankle is elevated while the patient is supine. (Using the aforementioned equation, the ankle pressure in millimeters of mercury [mm Hg] may be estimated as 0.74 times the height of the ankle above the bed in centimeters when flow is no longer detectable by Doppler.) Because digital arteries are less commonly involved with calcification, toe pressure measurements can be useful when ankle pressure is falsely elevated.<sup>31</sup>

## Segmental Pressures

An estimate of the level of disease in the lower extremity can be made by measuring blood pressure with cuffs placed at the arm, upper thigh, above-knee, below-knee, and ankle levels (Fig. 21.8). A Doppler device is used to detect blood flow at the ankle as each individual cuff is inflated and then slowly deflated. Typical segmental pressures from normal subjects and patients with various levels of occlusive disease are shown in Table 21.1. Upper thigh pressure is normally higher than brachial pressure, particularly when the relatively narrow, 10-cm standard thigh cuff is used. In this case, upper thigh pressure may be as high as or somewhat higher than brachial pressure,



**Figure 21.8** Segmental pressure is measured with the same technique as ankle pressure, but with cuffs placed at the upper part of the thigh, at the lower part of the thigh, below the knee, and at the ankle.

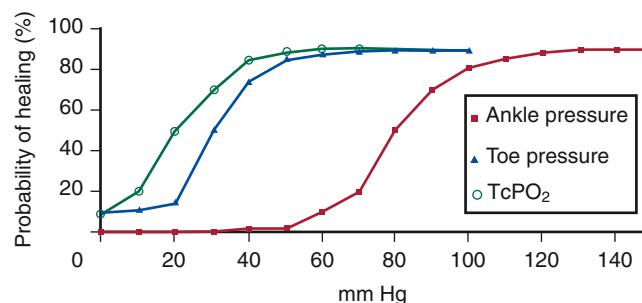
**TABLE 21.1** Typical Segmental Systolic Arterial Pressures (mm Hg)

	ARTERIAL DISEASE				
	Normal	Iliac	Superficial Femoral	Iliac and Superficial Femoral	Below-Knee
Arm	120	120	120	120	120
Upper thigh	160	110	160	110	160
Above knee	150	100	100	70	150
Below knee	140	90	90	60	140
Ankle	130	80	80	50	90

even in the presence of significant iliac disease. False-negatives may also result from restriction of outflow into the thigh because of occlusion of vessels by the cuff. The resulting limitation of flow across a stenotic iliac segment can prevent a pressure drop across it. A decrease in pressure of 20 mm Hg or more at any one level in comparison to the level above indicates significant disease. Because the most distal cuff is at the ankle, disease below this level is not detected.

Segmental pressure measurements do not detect disease in nonaxial vessels, such as the profunda femoris. Because of the difficulty in detecting stenoses when flow is restricted, multi-level disease can be difficult to identify when a proximal stenosis is causing a significant decrease in distal pressure and flow. Side-to-side comparisons should be made and are meaningful when there is a difference, but they may be misleading in patients with symmetric disease in the two extremities.

An estimate of the extent of collateralization around the knee in patients with superficial femoral artery occlusion can be made using the profundapopliteal collateral index (PPCI).<sup>32</sup> The PPCI is calculated as the difference between the above-knee and below-knee blood pressure divided by the above-knee pressure. A low index indicates good collateral development (little pressure drop across the knee). In general, a PPCI of less than 0.25 predicts a good result from profundaplasty without infrainguinal bypass, whereas a PPCI of greater than 0.50 predicts no improvement with profundaplasty alone.<sup>33</sup>



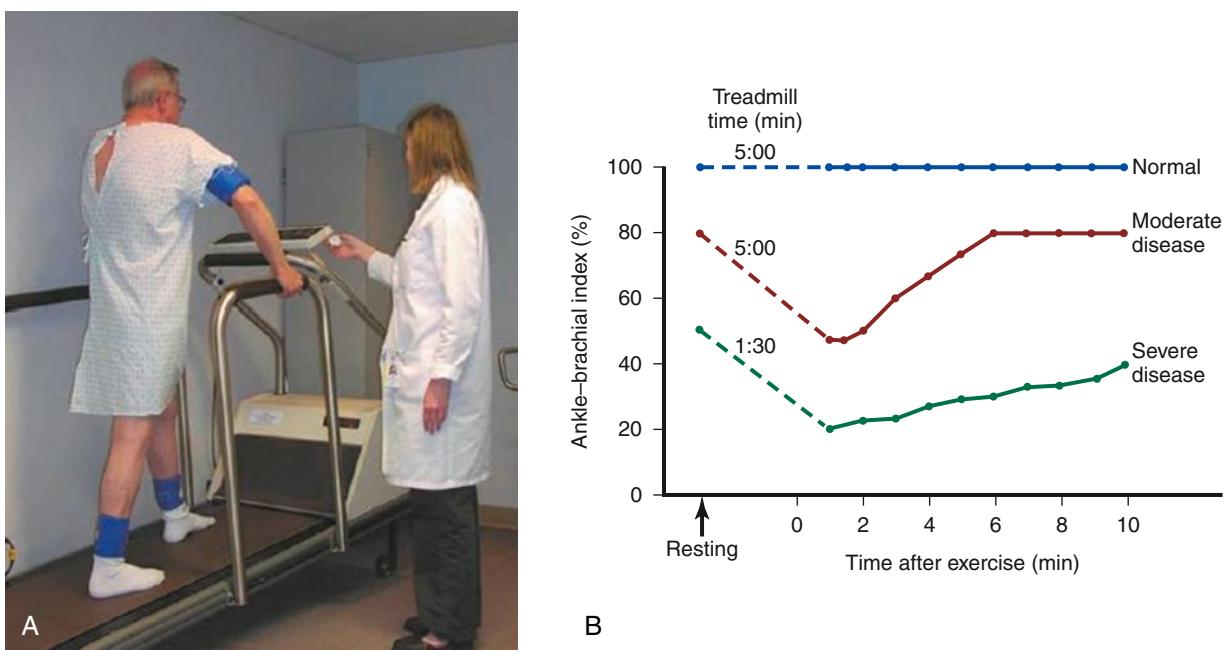
**Figure 21.9** A schematic estimate of the probability of healing of foot ulcers and minor amputations in relation to ankle blood pressure, toe blood pressure, and transcutaneous oxygen pressure ( $\text{tcPO}_2$ ) based on selected reports. (From Bakker K, Apelqvist J, Schaper NC; International Working Group on the Diabetic Foot Editorial Board. Practical guidelines on the management and prevention of the diabetic foot 2011. *Diabetes Metab Res Rev*. 2012;28:225–231.)

Use of segmental pressure does not add to simple ABI in improving the accuracy of Doppler waveform analysis in the diagnosis of PAD.<sup>34</sup> Segmental pressure measurement is frequently combined with pulse volume recording (see below) to provide a more accurate method for diagnosing PAD. Disadvantages include lack of exact anatomic detail, patient discomfort, and the potential to damage balloon-expandable peripheral arterial stents.

## Digital Pressure Measurement

Pressure in a digit can be measured in much the same way as arm and ankle measurements. An appropriately sized minicuff is placed around the base of the digit and attached to a standard manometer. Any type of flow detector can be used to determine when flow returns as the inflated cuff is slowly deflated. Most commonly used are photoplethysmography (PPG) probes and continuous wave Doppler flow detectors placed on the distal phalanx, but laser Doppler probes have also been used and may be more sensitive to extremely low flow.<sup>35</sup> As digital arteries are less commonly calcified than tibial arteries, toe pressures are most useful in patients prone to arterial calcification, such as diabetics and patients with chronic kidney disease. Toe pressure is also sensitive to disease at the level of the pedal arch and digital vessels, which is not detectable by ankle pressure measurements.<sup>36</sup> However, even digital arteries can be calcified and noncompressible, at which point waveform analysis or transcutaneous oxygen tension ( $\text{tcPO}_2$ ) measurements may be helpful (see Ch. 23, Techniques to Assess Tissue Perfusion in Peripheral Arterial Occlusive Disease).

Normal toe pressure is 20 to 40 mm Hg less than ankle pressure, possibly because of the measurement technique. A toe-brachial index less than 0.7 is considered abnormal.<sup>11</sup> Pressures of 30 mm Hg or lower are associated with ischemic symptoms (see Fig. 21.6B). Foot lesions usually heal when the toe pressure is greater than 50 mm Hg (or slightly higher in diabetics). The correlation between foot wound healing and toe pressure is shown in Figure 21.9. Unfortunately, toe pressures often cannot be obtained in patients with forefoot and digital gangrene for whom transmetatarsal amputation is contemplated (see Ch. 114: Lower Extremity Amputations: Epidemiology, Procedure Selection, and Rehabilitation Outcomes).



**Figure 21.10** (A) Patient undergoing a standard treadmill test. Pressure cuffs are left in position at the arms and ankles to allow immediate measurement on stopping. (B) Examples of exercise test results in patients with various degrees of peripheral arterial occlusive disease. The resting ankle–brachial indices are noted, followed by similar measurements immediately after exercise and for several minutes thereafter.

## Stress Testing

As noted above, the pressure reduction across a stenosis depends on the rate of flow through it. It is a useful, practical metric for quantitating the functional effect of arterial insufficiency. Exercise testing and reactive hyperemia are the two established methods.

### Exercise Testing

Because many patients with claudication and those with ischemic symptoms have decreased ABI at rest, exercise testing is only selectively required to diagnose PAD in the symptomatic patient with a normal resting ABI. This test is also useful to differentiate between true arterial claudication and neurogenic claudication or in the patient with both. It also helps to determine the extent to which cardiopulmonary, orthopedic, and vascular disease contributes to the patient's difficulty walking.

For standard exercise testing the patient rests supine for 20 minutes, after which resting ABI is measured. Blood pressure cuffs are left in position at both ankles and the upper extremities, and the patient is asked to walk at 2 miles/h on a treadmill at a 12-degree inclination for 5 minutes or until forced to stop because of symptoms (Fig. 21.10A). Note is taken of the time to initial symptom onset, the nature of the symptoms, and the time until stopping, which may be influenced by many factors, such as shortness of breath, patient motivation, and muscular pain. The patient is then asked to lie down, and ankle and arm pressures are measured immediately and then every 2 minutes for 10 minutes or until the pressure returns to resting levels.

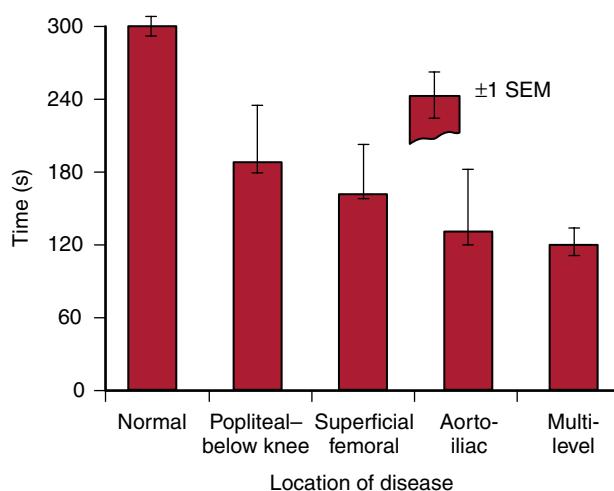
Clinically significant lower extremity PAD can be reliably ruled out in patients who can walk the entire time without symptoms or a decrease in the ABI. The severity of PAD is

reflected by the extent of the post-exercise drop and the length of time required to return to baseline levels (Fig. 21.10B). Patients with mild disease may have normal resting pressure but a mild drop in pressure after exercise that returns within minutes to baseline levels. Those with moderate to severe disease have abnormal resting ABIs with further decreases after exercise that persists throughout the post-exercise observation period of 10 to 15 minutes. Patients who have less than a 20-mm Hg pressure drop at the ankle in comparison with the upper extremity rarely benefit from vascular reconstruction. The exception to this is a patient with a mild or no arterial stenosis at rest and vasoconstriction induced by intense exercise as seen in iliac endofibrosis. A standard walking test does not result in a drop in ankle pressure in these young athletes; and a more intense exercise protocol may be required to elicit symptoms and a pressure drop.<sup>37</sup>

The treadmill test tends to be more positive with proximal disease than with distal disease (Fig. 20.11). The aortoiliac vessels supply all the musculature of the lower extremity, including the large muscular groups of the buttock and thighs, so the effect of lesions in these vessels is greater than the effect of isolated occlusion of an infringuinal vessel. Exercise testing is not effective for detection of disease below the level of the popliteal artery because the sural branches to the gastrocnemius muscle come off at or proximal to this level.

### Alternatives to Exercise Testing

In some cases exercise testing is not possible because of comorbid conditions or other factors precluding walking. In these situations, flow may be increased by reactive hyperemia or vasodilators. Reactive hyperemia is induced by occlusion of blood flow to the extremity by the tourniquet effect of a proximal blood



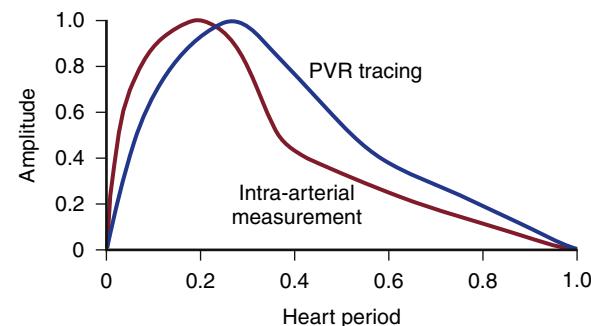
**Figure 21.11** Treadmill Walking Times in Patients with Occlusive Arterial Disease. Normal individuals can almost always exceed 5 minutes (300 seconds). (Modified from Strandness DE Jr, Sumner DS. *Hemodynamics for Surgeons*. New York: Grune & Stratton; 1975.)

pressure cuff inflated above the systolic pressure level for 3 to 5 minutes. When the cuff is released, peripheral vascular resistance is reduced, and flow is increased. This test is used infrequently because it is uncomfortable and does not produce sustained increases in flow. Reactive hyperemia can also be used to assess endothelial function in the brachial artery reactivity test.<sup>38</sup>

For the standard lower extremity reactive hyperemia test, a cuff placed around the thigh is inflated above systolic pressure for 3 to 7 minutes. After cuff deflation, ankle pressure is monitored two or three times a minute for up to 6 minutes or until measurements return to resting levels. In normal individuals, ankle pressure drops immediately to approximately 80% of resting levels but recovers within minutes to nearly normal levels. In patients with PAD the drop in pressure is approximately the same as that occurring after exercise, but recovery is more rapid, presumably because there is less oxygen debt. The magnitude of the drop in pressure correlates with the severity of disease, as does the length of recovery time, although less closely. This test has advantages over treadmill testing, such as being faster and less cumbersome, not needing a treadmill, not depending on patient motivation, being more easily standardized, and not being affected by cardiovascular or orthopedic conditions. Disadvantages include less specificity and sensitivity than exercise testing, patient discomfort, and more operator dependence because of the need for rapid pressure measurements, and it does not directly test the patient's ability to walk. These factors tend to outweigh the advantages of this technique, particularly because duplex scanning provides greater anatomic detail without patient discomfort.

### Direct Pressure Measurement

In some cases it is difficult to determine either by imaging or indirect testing whether a segment of artery has clinically significant narrowing. In such cases the most definitive test is direct pressure measurement, which can be done intraoperatively or at the time of percutaneous angiography. Vasodilators can be



**Figure 21.12** Comparison of pressure contours obtained with the pulse volume recorder (PVR) and direct cannulation of the common femoral artery. Axes normalized:  $y$  = fraction of maximal amplitude;  $x$  = fraction of one cardiac cycle. (Redrawn from Darling RC, Raines JK, Brener BJ, Austen WG. Quantitative segmental pulse volume recorder: a clinical tool. *Surgery* 1972;72:873–877.)

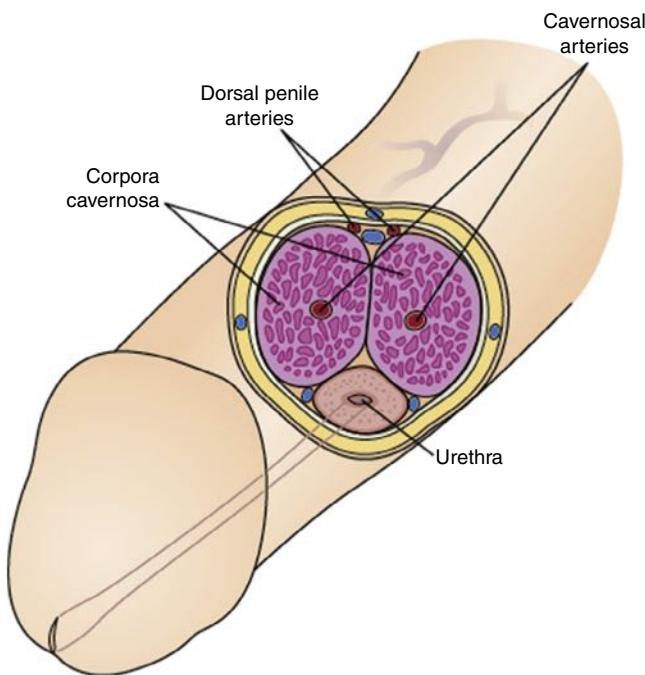
used when results are equivocal. Measurement of pressure along the course of a bypass can be a useful, rapid means of locating technical problems. The technique is simple. The artery at the level of interest (generally the common femoral artery when the aortoiliac segment is being assessed) is punctured with a 19-gauge needle and connected to a standard strain gauge with stiff tubing. When comparing with a reference pressure, such as the radial artery, the same pressure transducer is used to make it easy to switch between the two pressure lines and to eliminate errors that may be caused by having the two transducers at different heights. Direct pressure measurement is the gold standard to which indirect methods are compared (Fig. 21.12).

### Penile Pressure

Of the three paired penile arteries, which all arise from the internal pudendal artery (Fig. 21.13), the cavernosal artery is the most important for erectile function. Proximal occlusive disease can be responsible for vasculogenic impotence. Measurement of penile blood pressure is performed by applying a pneumatic cuff 2.5 cm in width to the base of the penis. Return of blood flow when the cuff is deflated can be detected by a mercury strain-gauge plethysmograph, a PPG probe applied to the anterolateral aspect of the shaft, or a Doppler flow probe. Although some investigators have positioned the probe over the dorsal penile arteries, others have emphasized the importance of detecting flow in the cavernosal artery.<sup>39</sup> Penile pressure and brachial pressure are normally equivalent, but penile–brachial index declines with age. Penile–brachial indices greater than 0.75 to 0.80 are considered compatible with normal erectile function; an index of less than 0.60 is diagnostic of vasculogenic impotence, especially in patients with peripheral vascular disease. A brachial–penile pressure gradient of less than 20 to 40 mm Hg suggests adequate penile blood flow. Gradients in excess of 60 mm Hg suggest arterial insufficiency (see Ch. 191, Erectile Dysfunction).

### PLETHYSMOGRAPHY

Plethysmography is based on measurement of change in volume of the extremity caused by the cyclic nature of arterial



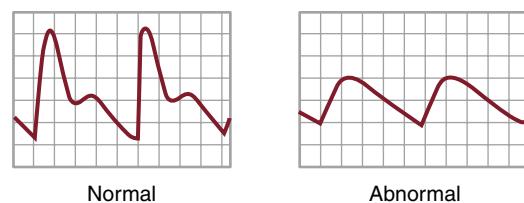
**Figure 21.13** The Paired Penile Arteries. (Urethral arteries not shown.)

inflow. The technique was developed using a mercury strain gauge placed around the extremity. Change in volume causes a change in circumference and therefore in the length and electrical resistance of the strain gauge. The resistance is easily measured and plotted on a strip chart, which results in a waveform that has the same basic contour as the pressure wave (see Fig. 21.12).<sup>40</sup> Impedance plethysmography works on similar principles; it monitors electrical impedance, which is inversely proportional to volume. These devices have largely been replaced by air plethysmography, which monitors pressure in a cuff placed around the extremity and inflated to 65 mm Hg, because the cuffs are more rugged and easier to use. Raines and colleagues, who developed these instruments, called them pulse volume recorders (PVRs).<sup>41,42</sup>

## Pulse Volume Recording

Like segmental pressure measurements, PVR waveforms obtained at various levels of the lower extremity can be used to infer the presence and location of arterial occlusive disease. The normal pulse contour has a rapid upslope, a sharp systolic peak, a dicrotic notch, and a downslope that bows toward the baseline (Fig. 21.14). Downstream from stenotic segments, the waveform becomes damped – the upstroke becomes less steep, the dicrotic notch is lost, and the overall amplitude is decreased. Thus a decrease in pulsatility (either the amplitude or upstroke) from one segment to the next indicates the presence of stenosis upstream. The extent of the changes in the waveform is related to the severity and extent of the proximal disease. Similar waveform changes may be also caused by downstream disease, confounding results.

Although the amplitude of the plethysmographic pulse is reduced by arterial occlusive disease, it alone is not a useful parameter for determining the extent of disease. Amplitude is



**Figure 21.14** Normal and abnormal pulse volume contours recorded at the ankle level. The normal form shows a prominent dicrotic wave on the downslope. Cuff pressure, 65 mm Hg; cuff volume, 75 mL.

**TABLE 21.2** Definition of Pulse Volume Recorder Categories

Category	CHART DEFLECTION (mm)		DV (mm <sup>3</sup> )		
	Thigh and Ankle	Calf	Ankle	Calf	Thigh
1	>15 <sup>a</sup>	>200 <sup>a</sup>	>160	>213	>715
2	>15 <sup>b</sup>	>20 <sup>b</sup>	>160	>213	>715
3	5–15	5–20	54–160	54–213	240–715
4	<5	<5	<54	<54	<240
5	Flat	Flat	0	0	0

<sup>a</sup>With reflected wave.

<sup>b</sup>No reflected wave.

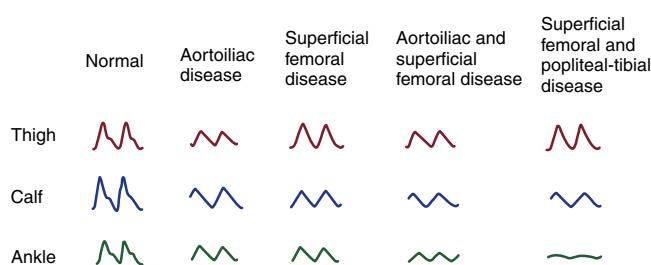
DV, maximal segmental volume change per heartbeat.

fairly constant within an individual; however, intersubject variability is large because of differences in body and limb size, blood pressure, peripheral resistance, and cardiac output. A classification scheme has been devised to rate arterial disease from normal (1) to mild (2, 3) to severe (5), based on amplitude and changes in the waveform (Table 21.2). Pulse amplitude increases in normal limbs after exercise. As with pressure measurements, waveform contours that are normal at rest may become abnormal with increased flow. Flow-limiting stenosis causes deterioration of the waveform and reduction of the PVR amplitude at the ankle. PVR tracings from limbs with various combinations of disease are shown in Figure 21.15.

PVR is less affected than pressure measurements by arterial calcification. The combination of segmental pressure measurements and PVR is more accurate than either method alone for detecting PAD.<sup>43</sup> There is current debate regarding whether these indirect physiologic tests should be completely replaced with arterial duplex scanning; however, they require less technologist expertise, allow assessment of the adequacy of the collateral circulation, and may be more appropriate for screening purposes.

## Digital Plethysmography

As noted above, digital pressure measurements are useful when calcification of tibial vessels causes false elevations in ankle pressure or when patients have occlusive disease distal to the ankle level. The PPG probe commonly used for this application sends an infrared light into the tissue and has a detector



**Figure 21.15** Pulse volume recorder tracings from a normal limb and from limbs with various combinations of peripheral vascular disease. (Modified from Rutherford RB, Lowenstein DH, Klein MF. Combining segmental systolic pressures and plethysmography to diagnose arterial occlusive disease of the legs. *Am J Surg*. 1979;138:216.)

for backscattered light that corresponds to the variation of blood volume over time.<sup>44</sup> The pulse oximeter is a form of PPG probe.

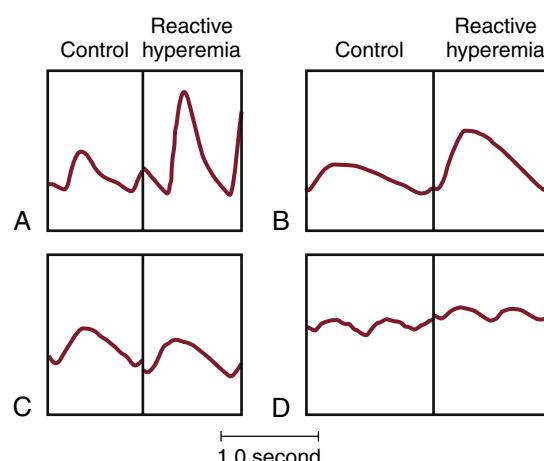
### Pulse Contour

Changes in the plethysmographic waveform in the digit reflect any proximal disease. Significant disease documented by digital pressure and abnormal plethysmographic waveforms may be present despite adequate ankle pressure. Digital PVR is also useful for determining the extent of sympathetic activity in patients with cold sensitivity or the presence of significant steal syndrome caused by dialysis access grafts. Comparison of waveforms and digital pressures with and without access flow occlusion demonstrates the hemodynamic effects of the access. The pulse contour in the digits is similar to that described previously for the lower extremity with the normal waveform having a rapid upslope, a sharp systolic peak, a dicrotic notch, and a downslope that bows toward the baseline. Occlusive disease causes dampening of the waveform with flattening and loss of the dicrotic notch. In extreme cases there may be no detectable waveform. Conversely, the presence of a normal digital waveform indicates that there is no clinically significant arterial disease in the arteries supplying the digit.

### Reactive Hyperemia

Because resistance vessels in extremities with significant flow-limiting PAD are already maximally dilated to compensate for reduced flow, there is little additional response to reactive hyperemia. A cuff is placed at the ankle or above, inflated above systolic pressure for 3 to 5 minutes, and rapidly deflated while the digital PVR is monitored. In normal limbs the pulse returns rapidly, attains half its baseline amplitude within a few seconds, and then rises quickly to twice baseline (Fig. 21.16A). With PAD, reappearance of the waveform and return to half the resting value are markedly delayed in proportion to the severity and extent of the disease (Fig. 21.16B–D, Table 21.3).

The response to reactive hyperemia requires resting sympathetic tone. Therefore this test is useful for predicting the response to sympathectomy, which increases blood flow by decreasing peripheral resistance. If the increase in PVR amplitude is less than twice the resting level, sympathectomy likely will not improve skin blood flow. However, the response to reactive hyperemia is not dependent on intact sympathetic innervation,



**Figure 21.16** Reactive Hyperemia Test; Digit Pulse, Second Toe. Digit pulse volume more than doubles with a normal response (upper panels). Little hyperemic response in pulse volume is evident with an abnormal response (lower panels). (A) Normal circulation. (B) Superficial femoral occlusion. (C) Diabetic for 20 years. (D) Iliac and superficial femoral arterial disease.

so this test cannot be used to determine if the sympathetic nerves are intact. Instead the deep breath test can be used for this purpose. Sympathetic innervation is intact if there is a decrease in pulse volume in response to a deep breath.

## OTHER METHODS

Several methods can be used to evaluate the effects of PAD on the microcirculation, including tcPO<sub>2</sub>, laser Doppler, hyperspectral imaging, cold testing, vasoreactivity, and capillaroscopy<sup>45,46</sup> (see Ch. 23, Techniques to Assess Tissue Perfusion in Peripheral Arterial Occlusive Disease).

### Transcutaneous Oxygen Tension

TcPO<sub>2</sub> measurements reflect the metabolic state of the target tissues. Electrodes containing a circular silver-silver chloride anode surrounding a central platinum cathode are placed on the skin at the dorsum of the foot, the anteromedial aspect of the calf 10 cm below the patella, and the thigh 10 cm above the patella. The subclavicular region of the chest has been used as a reference site to calculate a regional perfusion index in an effort to control for variation caused by age, cardiac output, and arterial partial pressure of oxygen (PO<sub>2</sub>). This index is not widely used. Oxygen diffusing to the surface of the skin is reduced at the cathode to produce a current proportional to the PO<sub>2</sub> within the sensor. The electrode has a heating element that raises the skin temperature to 45°C for optimal blood flow and diffusion of oxygen, from vasodilatation, rise in capillary PO<sub>2</sub>, liquefaction of lipids in the stratum corneum, and a right shift in the oxyhemoglobin dissociation curve.<sup>47</sup>

Transcutaneous oxygen measurement is relatively insensitive to mild or moderate degrees of PAD because the oxygen supplied to the skin is far greater than the demand. Furthermore, because the oxyhemoglobin dissociation curve does not change rapidly until oxygen saturation drops to less than 80%, capillary oxygen tension does not decrease until inflow

**TABLE 21.3****Pulse Reappearance Time After Release of Arterial Occlusion**

Location of Occlusive Disease	Pulse Reappearance Time (s)	Time Required to Reach Half Control Volume (s)
No occlusion	0.2 ± 0.1	3.4 ± 0.8
Aortoiliac	7.2 ± 4.0	23.9 ± 6.7
Femoropopliteal	3.7 ± 3.7	26.5 ± 12.7
Popliteal trifurcation	15.2 ± 9.3	23.9 ± 9.4
Multilevel	45.3 ± 5.5	71.2 ± 5.5

Modified from Fronek A, Coel M, Bernstein EF. The pulse-reappearance time: an index of over-all blood flow impairment in the ischemic extremity. *Surgery*. 1977;81:376.

is severely restricted and oxygen demand equals or exceeds supply. When values are low, tcPO<sub>2</sub> is not linearly related to flow. A value of zero means all the available oxygen has been consumed rather than the absence of flow. Measurement of tcPO<sub>2</sub> must be interpreted cautiously as it is affected by many factors that are difficult to measure or to control and therefore is unreliable (Box 21.1). For this reason and because the method is time consuming, it has not gained wide popularity. Measurement of tcPO<sub>2</sub> is most helpful for evaluating cases of severe ischemia, particularly when determining the optimal level for amputation. It is especially useful in diabetic patients because it is not affected by arterial calcification. Normal tcPO<sub>2</sub> values depend on age (higher for younger patients) and position (higher for more proximal locations). In general, values greater than 55 mm Hg are considered normal. Proximal locations are less sensitive than more distal locations to PAD, with the foot being the most sensitive. Wound healing is not reliable when the local tcPO<sub>2</sub> is between 20 and 40 mm Hg (see Fig. 21.9).<sup>48</sup>

Various enhancement procedures have been proposed to improve the discriminative value of tcPO<sub>2</sub>. Among these are observing the change in tcPO<sub>2</sub> with dependency.<sup>49</sup> Advanced disease is associated with a larger increase when the patient moves from the supine position to sitting or standing. This increase in tcPO<sub>2</sub> may be related to the increased hydrostatic pressure that dilates capillaries and resistance vessels, thereby increasing flow. This phenomenon may explain why dependency relieves rest pain.<sup>50</sup> Exercise is followed by a decrease in skin tcPO<sub>2</sub> because of shunting of blood away from the foot by dilatation of intramuscular vessels. The tcPO<sub>2</sub> response to hyperemia is similar to that of ankle pressure; it decreases after inflow obstruction and is much slower to recover in patients with severe PAD. Finally, oxygen inhalation has been used in attempts to improve the accuracy of tcPO<sub>2</sub> for determining the amputation level and predicting the effectiveness of hyperbaric oxygen therapy. A greater than 10 mm Hg increase after the inhalation of 100% oxygen is considered normal.<sup>51</sup> Patients with severe PAD have a much smaller increase in tcPO<sub>2</sub> than do normal individuals upon oxygen inhalation.

**BOX 21.1****Factors Affecting Transcutaneous Oxygen Tension**

Skin temperature	Oxygen diffusion through tissue
Sympathetic tone	Oxyhemoglobin curve
Body temperature	Increased venous pressure
Cellulitis	Vertical position of the site of measurement relative to the heart
Hyperkeratosis	Age
Obesity	
Edema	
Metabolic activity	

**Laser Doppler and Skin Perfusion Pressure**

The laser Doppler uses monochromatic light to detect motion of red blood cells to a depth of approximately 1.5 mm in the skin.<sup>52</sup> The actual depth depends on the power of the laser beam, the thickness of the epidermis, and skin pigmentation. Light is backscattered by the tissues after transmission and again after it is reflected back to the receiving system. As a result the frequency shifts are a composite of multiple vessels with multiple velocities and multiple angles. The output, measured in millivolts, is approximately proportional to the average blood flow in a 1.5-mm<sup>3</sup> volume of skin lying 0.8 to 1.5 mm below the skin surface. The signal tracing has pulse waves that coincide with the cardiac cycle and vasomotor waves at a frequency of four to six times per minute. The instrument cannot be calibrated to give an exact estimate of blood flow because of the multiple factors that affect the signal. It is useful when only qualitative information is needed.

Resting values in the lower extremity vary anatomically and are highest in the great toe and lowest in the proximal part of the leg. PAD causes attenuation of the waveform, a reduction in velocity, and loss of vasomotor waves. Like tcPO<sub>2</sub> and ankle pressure, the response to hyperemia is diminished, and the time to recovery is increased. The ability of this test to predict amputation healing is not as good as that of transcutaneous oxygen measurements. Laser Doppler can be used with blood pressure cuffs to measure skin perfusion pressure.<sup>53</sup> The probe can be placed distally as a flow detector for similar results in obtaining segmental pressures, or beneath the cuff, which is then inflated. The pressure at which skin blood flow returns is noted as the cuff is slowly deflated. Normal pressures of 50 to 70 mm Hg are decreased to 10 to 20 mm Hg with significant PAD. Pressures less than 30 mm Hg are predictive of critical limb ischemia.<sup>53</sup> A combination of skin perfusion pressure greater than 40 mm Hg and toe blood pressure greater than 30 mm Hg has been associated with successful lower extremity wound healing.<sup>54</sup>

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