

landing zones allowed for appropriate sealing of the aneurysm proximally and distally.<sup>52</sup> In patients with drug-eluting stent placement for treatment of femoropopliteal lesions, IVUS guidance and post-procedural IVUS assessment was able to offer predictors of restenosis at 1 year.<sup>53</sup> In another study, IVUS use was associated with higher primary patency rates following nitinol stenting of TASC II A-C lesions.<sup>54</sup> Multiple recent studies continued to demonstrate the importance of IVUS use in PAD. Sheikh et al. compared the outcomes of IVUS and angiography-guided peripheral vascular interventions (PVI) and showed no difference in the rate of intervention but lower risk of peri-procedural events and vascular complications in the IVUS group.<sup>55</sup> In another study, Pligas et al. showed that measurements obtained from angiographic images were significantly smaller than those obtained by IVUS.<sup>56</sup> Shammas et al. showed the superiority of IVUS in identifying post atherectomy dissections when compared to angiography while Yin et al. showed that IVUS was significantly superior to angiography in detecting calcium in lesions.<sup>57,58</sup> Moreover, Krishnan et al. showed lower target lesion revascularization at 1 year in IVUS-guided vs. angiography-guided atherectomy.<sup>59</sup> As these studies demonstrate, the information provided by IVUS has shown clear benefits in treatment of the peripheral vasculature and the authors of this chapter support the liberal use of IVUS in the majority of peripheral vascular interventions.

### Intravascular Ultrasound-Guided True Lumen Reentry

Endovascular revascularization to recanalize peripheral arteries is often unsuccessful because of a failure to reenter the true lumen after crossing an occlusion in the subintimal plane. Use of a device such as the Pioneer Plus,<sup>60</sup> which combines IVUS with reentry technology, can ensure true lumen reentry and improve outcomes, as shown in several studies. In one study of patients with chronic total occlusion of the iliac arteries, the use of the Pioneer device (a precursor to the Pioneer Plus) was able to decrease procedure time and improve precision of reentry, resulting in improved technical success of the recanalization procedure.<sup>61</sup> Another study found similarly positive outcomes in longitudinal follow-up of use of IVUS reentry devices for iliac and infrainguinal chronic total occlusion (CTO).<sup>62</sup> Use of IVUS in conjunction with reentry devices ensures accurate needle placement and reentry.

### Carotid Applications

IVUS can also be useful in the treatment of carotid arteries. A study of endarterectomy patients found that use of IVUS allowed correct identification of the distal ends of stenotic lesions, increasing the amount of information available to physicians that may not have been initially available with preoperative angiograms.<sup>63</sup> Similarly, a study of patients undergoing carotid angioplasty and stenting found that IVUS provided complementary information to allow more detailed characterization of lesions and thus to inform choice of type and size of stent.<sup>64</sup>

## Endovascular Repair: Abdominal Aortic Aneurysms

### Preoperative Intravascular Ultrasound

Abdominal aortic aneurysms (AAA) are increasingly being treated endovascularly.<sup>65,66</sup> Preoperative planning for such procedures requires high-quality imaging to characterize arterial morphology, particularly for accurate assessment of landing zones proximally and distally. Most of this planning is done using CTA. However, the use of IVUS preoperatively may be beneficial in several instances. It has been shown that IVUS provides accurate measurements of the length and diameter in landing zones, aiding in the proper selection and sizing of endografts.<sup>67,68</sup> In the case of patients with tortuous vessels, the combination of information from IVUS and CTA preoperatively can improve the ability to accurately assess and plan for cases that may be technically challenging.

### Intraoperative Intravascular Ultrasound

For patients with abdominal aortic aneurysm, IVUS is most effectively used intraoperatively. Prior to stent graft deployment, IVUS can help to assess access anatomy in patients with questionable suitability for percutaneous endografting as seen on CTA. Prior to endograft delivery in patients with difficult access, IVUS can guide rotational atherectomy or balloon angioplasty, or balloon lithotripsy, or determine whether a conduit may be necessary. This assessment of access vessels can limit complications such as iliac dissection or rupture. During deployment, IVUS can visualize side branches for accurate placement of the graft. In the event that a bifurcated graft is being deployed, IVUS can also be used to ensure that the contralateral gate has been properly cannulated.

### After Repair

After deployment of the stent-graft, IVUS can determine the completeness of treatment by assessing apposition to the vessel walls proximally and distally as well as apposition between overlapping stent-grafts. Potential endoleaks can thus be visualized and characterized. The use of IVUS for immediate intraoperative assessment of treatment can facilitate decision-making about the necessity of further interventions such as ballooning, placement of proximal cuffs, or additional stent grafts, thus preventing the need for later reinterventions.

## Endovascular Repair: Thoracic Aortic Disease

Endovascular thoracic aortic stent grafts are being used to treat a variety of thoracic aortic pathologies, including aneurysm, dissection, penetrating aortic ulcer (PAU), intramural hematoma (IMH), coarctation, and thoracic aortic injury secondary to trauma.<sup>69–72</sup> IVUS can clearly identify and characterize all those pathologies along with providing additional information that may not have been provided in CTA imaging. Unlike imaging for abdominal aortic pathologies, CTA imaging for thoracic disease often does not include abdominal and pelvic visualization. IVUS can therefore be used to provide information about access sites. Thoracic grafts often require larger

sheath diameters, thus increasing the risk for access-related complications and the need for accurate assessment to evaluate need for a conduit or additional treatment prior to delivering the main graft. IVUS can also provide information about arch vessel involvement that may not have been available on CTA, informing decisions about landing zones and any additional stenting that may be necessary.

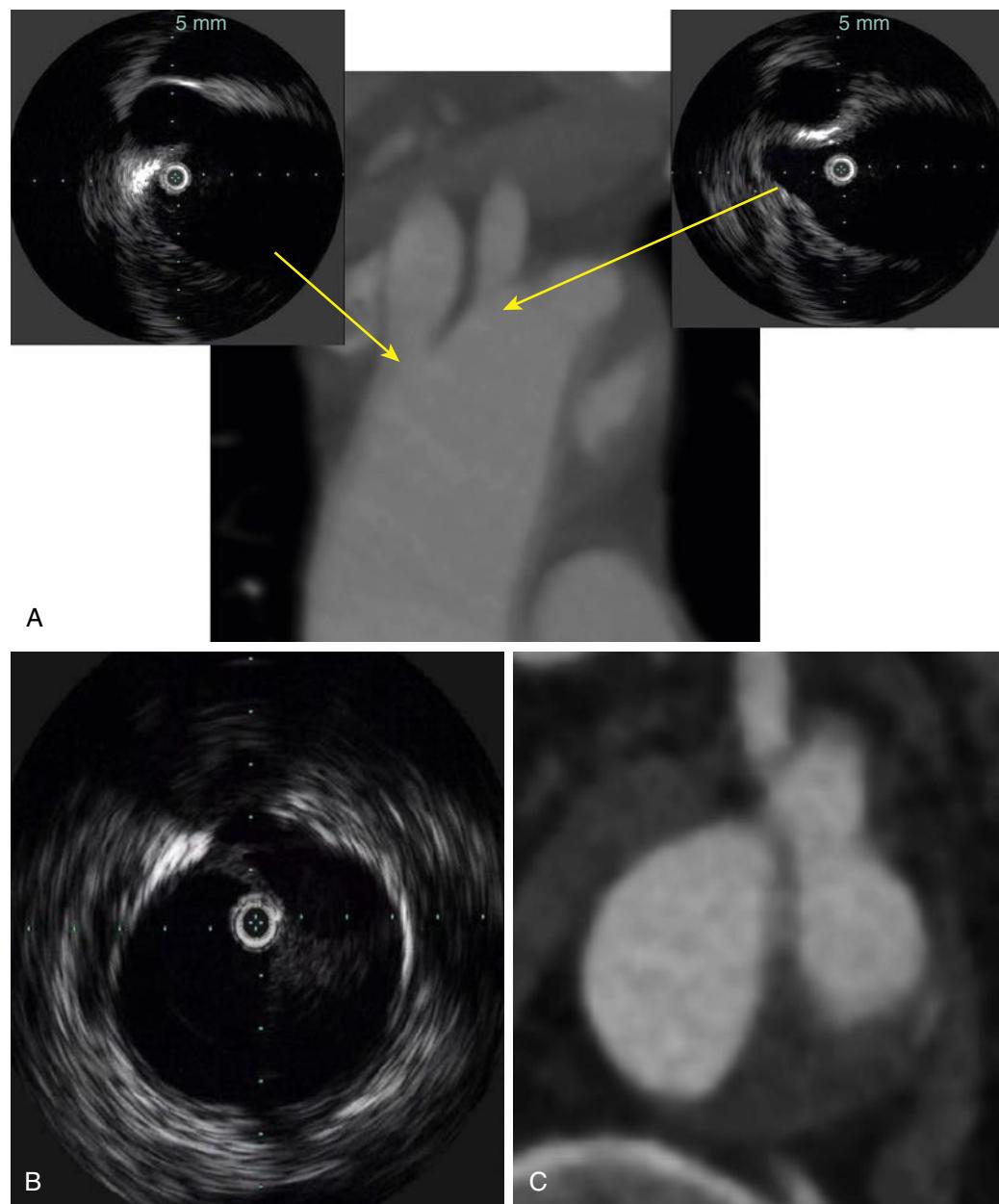
### Thoracic Aneurysms

The benefits of IVUS use in the treatment of thoracic aortic aneurysm are similar to the benefits provided in the treatment of abdominal aortic aneurysm, with the addition of the aforementioned benefits that are general to IVUS use in thoracic aortic disease. Before intervention, it can assess the access vessels, determine the amount of graft coverage necessary, guide

graft sizing, and identify branch vessels and landing zones (Fig. 32.6 and Video 32.2). Of note, IVUS is especially beneficial in detecting any sources of potentially embolic material, such as calcific plaques or mobile atheroma in the aortic arch. This can allow physicians to limit ballooning in the arch in order to reduce the risk of embolic stroke.<sup>73</sup>

### Blunt Traumatic Aortic Injury

Although CTA remains essential as a diagnostic tool for blunt traumatic aortic injuries (BTAs), such as rupture, intimal tears, or transection, additional imaging is sometimes required. A study of BTAI patients with equivocal CTAs found that IVUS was more sensitive than angiography in these cases, with 3 out of 25 patients having had a negative angiogram being diagnosed only by IVUS.<sup>74</sup> Additionally, the aortic diameter in



**Figure 32.6 Branched Vessels.** On IVUS, it is possible to see the take-off of the great vessels (A, arrows indicate location of IVUS images captured at innominate and carotid arteries). IVUS image (B) and correlating CTA (C) show the celiac artery perfused by a partially thrombosed false lumen.

**Video 32.2** IVUS pullback from ascending aorta all the way back to just below the renal arteries showing all the branches in between.

patients with traumatic aortic injury often increases from the time of initial CTA to the time of repair due to hypovolemic shock and subsequent resuscitation, thus highlighting the need for intraoperative reassessment and real-time measurement to guide device sizing.<sup>75</sup> This accurate sizing of the true aortic luminal diameter can prevent graft infolding or bird-beak configuration and ensure proper wall apposition.<sup>76</sup> This is especially critical for BTAI patients, who are often younger, necessitating the anticipation of changes that come with aging and appropriate planning to promote longer-term durability of treatment.<sup>77</sup>

### Coarctation

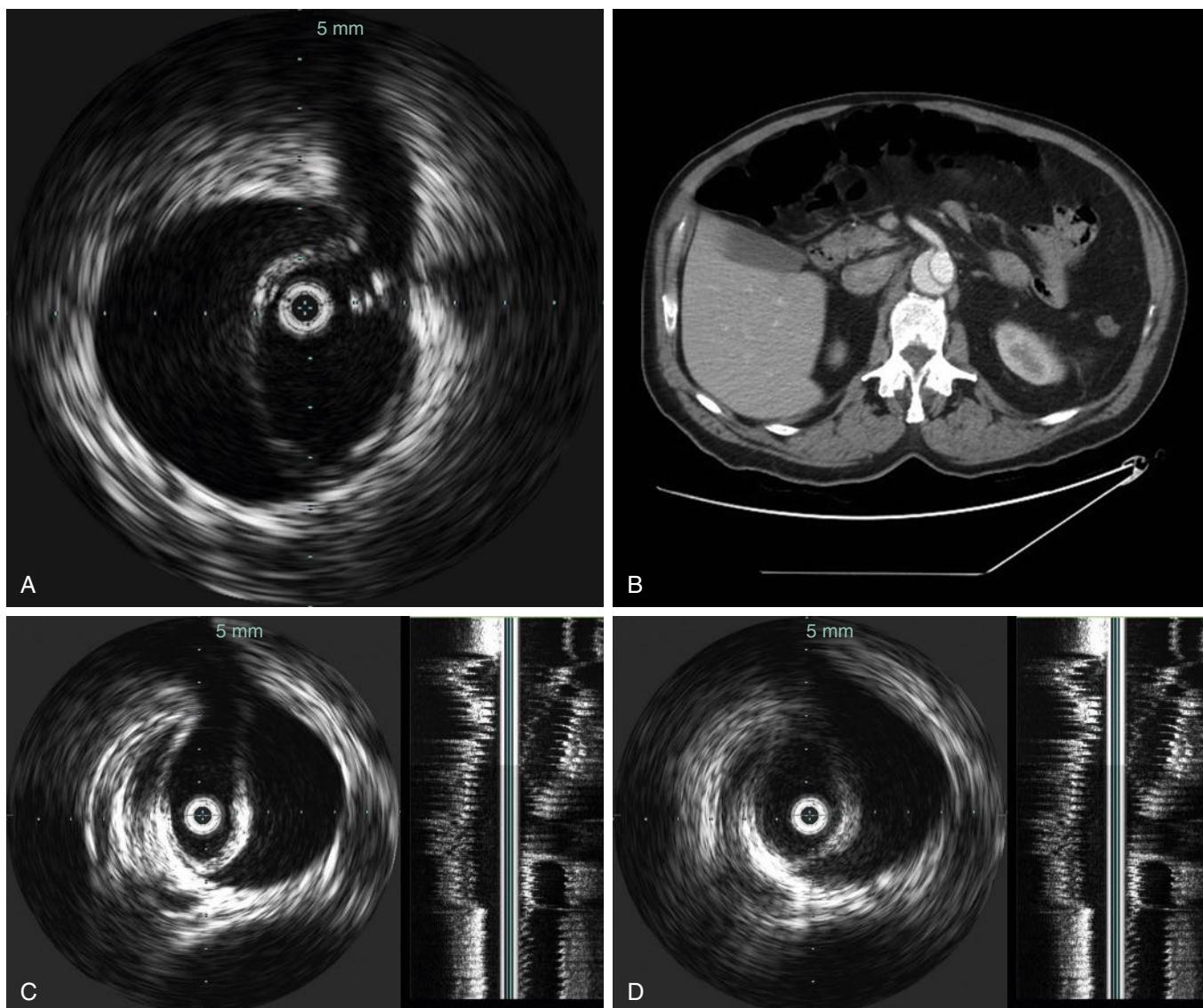
IVUS has emerged as an important imaging technique in endovascular repair of coarctation of the aorta. In a study examining balloon dilation for native and recurrent coarctation of the aorta, it was found that IVUS was more sensitive than angiography in providing detail regarding vascular wall changes,

remodeling, and intimal tears.<sup>78</sup> Not only useful intraoperatively, IVUS may be beneficial in the diagnosis of arch anomalies or coarctation. In 2000, a total of 20 infants and children with arch anomalies were examined, and it was determined that it is possible to diagnose arch anomalies accurately using IVUS catheters from a transesophageal approach with three-dimensional image reconstruction.<sup>79</sup>

### Dissection

#### Pre- and Intraoperative Intravascular Ultrasound

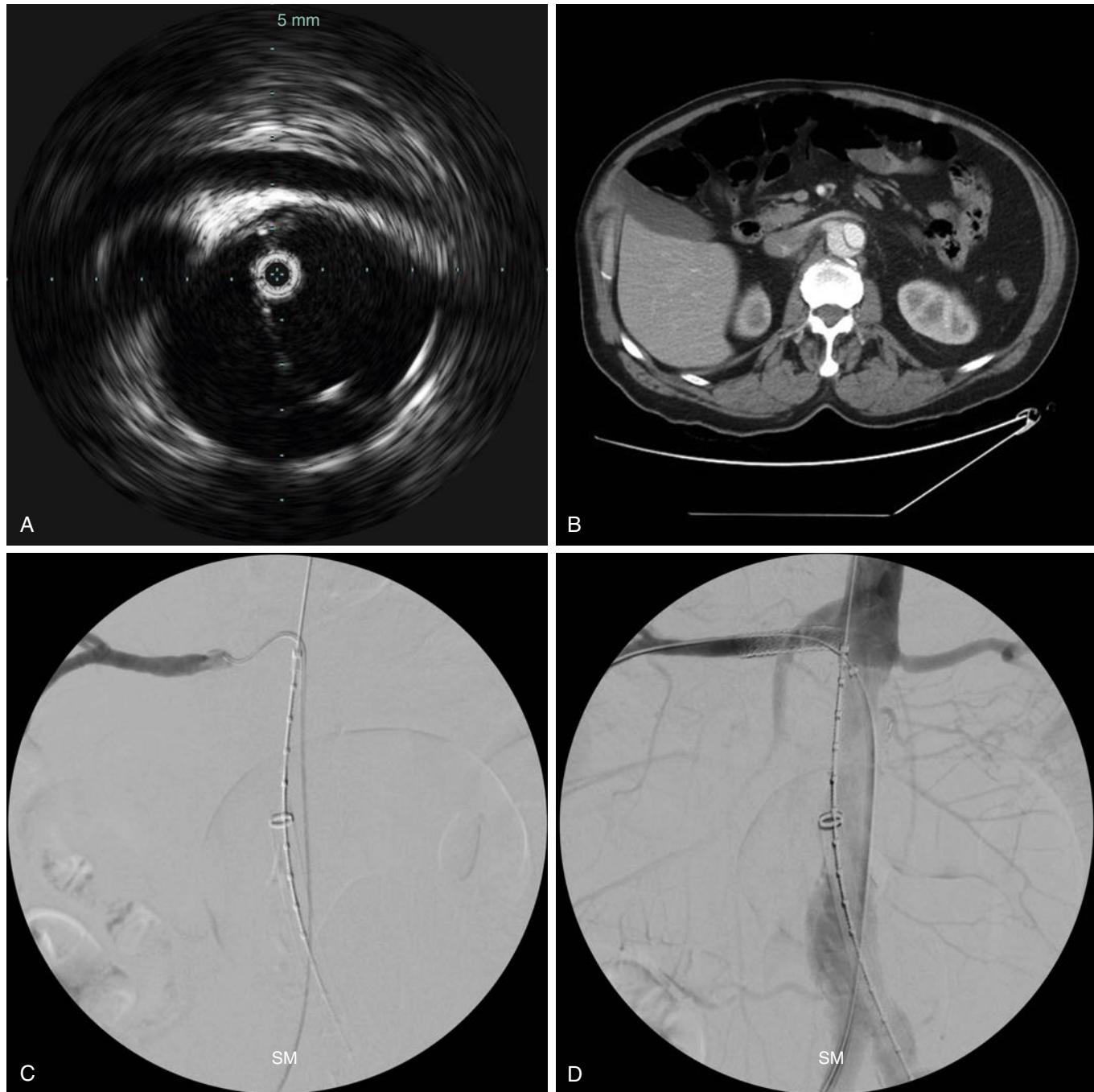
The benefit of IVUS in endovascular treatment of thoracic aortic dissections is most clearly seen in its ability to identify the true and false lumens (Fig. 32.7). Characterization of the dissection is also possible, with the ability to identify the entry tear and other fenestrations between the true and false lumen. Movement and thickness of the dissection flap can be



**Figure 32.7** (A) It is possible to see the intima separating the true and false lumens and the superior mesenteric artery (SMA) coming off the true lumen. (B) Computed tomography angiography of dissection and SMA coming off true lumen. (C,D) Dynamic obstruction as seen on intravascular ultrasound with longitudinal reconstruction.

visualized, facilitating the diagnosis of dynamic obstruction due to flap motion (Videos 32.3 and 32.4). The benefit of IVUS in treating Stanford type B dissections, especially “complicated” type B dissections, is clear in its ability to identify visceral vessels.<sup>80</sup> Not only can dynamic obstruction be clearly seen, but it is also possible to assess through which lumen each artery is perfused, guiding further therapies if visceral stents are required (Fig. 32.8). Identification of the celiac artery with IVUS can also assist in placement of the graft, as the origin of this artery is sometimes difficult to identify solely with aortography.<sup>81</sup>

Because it provides accurate measurements of vessel diameter and exact locations of branch vessels and fenestrations, the use of IVUS in treating dissections can facilitate the identification and characterization of proximal and distal landing zones, determine the amount of coverage required, and guide selection of the appropriate size and length of device to be used. As in other aortic pathologies, IVUS can also guide wire navigation. This is especially important in the case of dissection, as it is difficult to determine by angiography alone whether a wire is in the true or false lumen. IVUS thus becomes especially useful in



**Figure 32.8** (A) The right renal artery coming off the false lumen. (B) Computed tomography angiography of dissection with the right renal artery coming off the false lumen. (C) Selective cannulation of the right renal artery. (D) Final placement of graft across the septum of the false lumen into the true lumen.

**Video 32.3** IVUS showing flap motion in a patient with type B aortic dissection.

**Video 32.4** IVUS showing dynamic obstruction of the origin of the superior mesenteric artery due to flap motion in a patient with type B aortic dissection.

appropriately guiding wires into the arch, because it can confirm true lumen access. Where percutaneous fenestration of the intimal flap becomes necessary, IVUS may also guide this therapy.<sup>82</sup>

### After Deployment

After device deployment, IVUS can assess the completion and success of treatment. In Stanford type B dissections, IVUS can be used to examine the proximal deployment zone of the stent-graft and ensure that arch vessels are patent. It can also assess the ascending aorta for the presence of a retrograde dissection. IVUS can also be beneficial in the further evaluation of visceral vessels after the main stent-graft has been deployed, as it can identify continued malperfusion and guide further treatment. Postoperatively, expansion of the true lumen can be determined and the false lumen assessed for extent of thrombosis. In the case of type A dissections, IVUS has also been shown to be valuable in follow-up for patients with ascending arch replacement.<sup>83</sup>

### Penetrating Aortic Ulcers and Intramural Hematoma

As with dissection, IVUS can be beneficial in the treatment of PAU and IMH.<sup>84,85</sup> The exact location and size of the ulcer can be visualized with IVUS, allowing appropriate proximal and distal landing zones to be determined. As in the treatment of other aortic pathologies, this information guides the choice of appropriate graft size and length. In the case of IMH, IVUS is especially useful in visualizing the arterial wall and distinguishing the intima and adventitia, allowing appropriate sizing to be performed. After intervention, stent apposition can be clearly seen, ensuring that the ulcer is completely covered.

### Venous Imaging and Applications

The ability of IVUS to characterize the extent and composition of lesions and provide information about vessel morphology is well documented in arterial and aortic pathology. However, IVUS is also well suited to the particular needs of venous imaging and has advantages over both single and multiplanar venography.<sup>86,87</sup> Although venography can characterize hemodynamics and visualize secondary veins, it does not allow for dynamic imaging, cannot accurately evaluate intraluminal pathologies, and does not provide accurate sizing information.

Montminy et al. compared IVUS and venography to determine parameters for iliac vein stenting. They showed that venography missed the location of maximal stenosis in more than two-thirds of patients and misidentified the caval confluence and distal landing zones. The median maximal stenosis was significantly higher in IVUS.<sup>88</sup> In another study, IVUS identified stenotic lesions not detected by venography in 26.3% of patients and changed the treatment plan in 57% of patients.<sup>89</sup> IVUS can also identify plaque morphology, trabeculae and intraluminal webs, neointimal hyperplasia, degree of thrombosis, immobile or inverted valves, and other deformities and abnormalities.<sup>90</sup> It can also provide measurements that may be difficult to obtain with venography. This is especially important in treatment of veins, since veins often have irregular circumferences and unusual contours, making the analysis of stenoses

and vessel diameters difficult. By measuring cross-sectional areas and diameters of veins and evaluating the degree of disease or compression, IVUS can guide treatment and assist in the sizing of balloons or stents.

In fact, IVUS measurements of stenosis and post-procedural stenotic change were predictors of clinical improvement, while venogram measurements were not.<sup>91</sup>

### Venous Thromboembolism

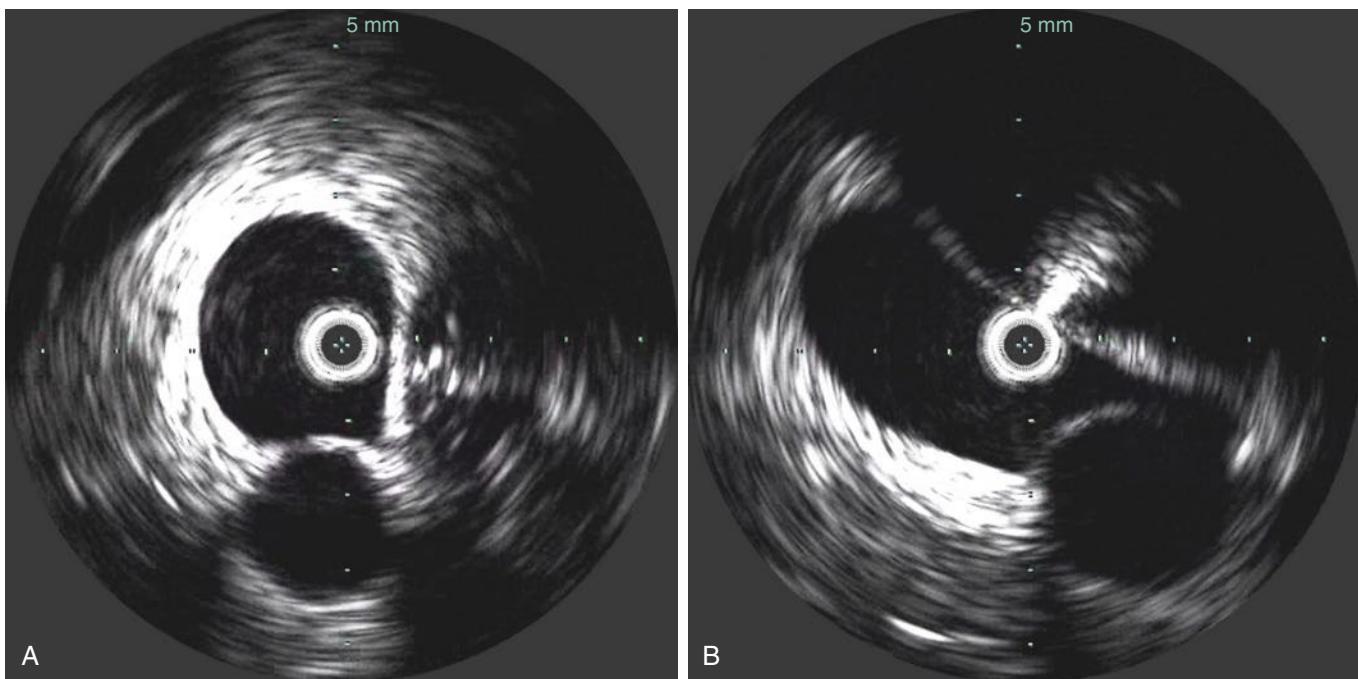
In the case of deep venous thrombosis, IVUS can be useful in providing additional diagnostic imaging to identify lesions that may not be visualized by venography.<sup>92,93</sup> It has also been shown to be more sensitive than venography in detecting residual thrombus, thus recommending its routine use in thrombolytic regimens.<sup>94</sup> However, IVUS is more frequently utilized to treat venous thromboembolism in the inferior vena cava than in the peripheral vessels. Because IVUS can obtain accurate sizing measurements and identify branch vessels, it can guide the placement of filters.<sup>95</sup> Recent studies examining the use of IVUS instead of contrast venography for the placement of inferior vena caval (IVC) filters have found it to be a safe and effective technique.<sup>96</sup> Additionally, IVUS guidance in placing IVC filters can also eliminate the need to transport patients to an endovascular suite.<sup>97</sup> These benefits can be significant, especially for critically ill patients, as bedside IVC filter placement reduces the amount of contrast or fluoroscopy required while also eliminating the need for patient transfer.

### Chronic Cerebrospinal Venous Insufficiency

As in other venous applications, IVUS aids in the diagnosis and treatment of chronic cerebrospinal venous insufficiency (CC-SVI) because of its ability to assess and characterize vessel size and intraluminal abnormalities. The ability to evaluate valve abnormalities and endoluminal structures and constrictions is especially important in visualizing the jugular and azygos veins, as the nature of stenoses detected in major cerebrospinal veins is not always clearly seen in venography.<sup>98</sup> On IVUS, abnormal valves are easily seen because of the high echogenicity of thickened areas. One study assessing the accuracy of catheter venography as compared with IVUS and color Doppler (CD) sonography found that catheter venography was inferior to both IVUS and CD sonography in detecting jugular endoluminal malformations and that CD sonography underestimated the cross-sectional areas of internal jugular veins (IJV) as compared with IVUS.<sup>99</sup> Especially for the treatment of stenosis in the IJV, accurate sizing is difficult to obtain owing to the vessel's lack of a uniform circular shape. IVUS can therefore aid in proper balloon sizing, traditionally a challenge in treating IJV stenoses, and prevent complications secondary to improper sizing.

### Venous Compression Syndromes

The use of IVUS in venous compression syndromes can allow for improved diagnosis and more effective treatment (Fig. 32.9). In studies of patients with May–Thurner syndrome, it was found that IVUS had a higher success rate than venography in identifying obstructions and in many cases was able to confirm



**Figure 32.9** Intravascular ultrasound demonstrates an uncompressed vein (A) and a vein compressed by an artery (B) in venous compression syndrome.

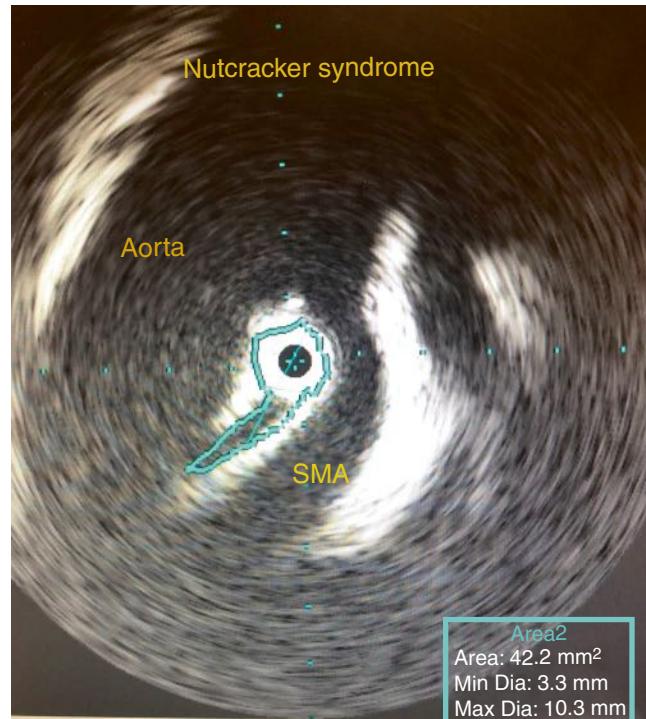
diagnosis and influence endovascular management.<sup>100,101</sup> Similarly, a study evaluating IVUS and venography for patients with lower extremity venous stasis disease and for iliofemoral vein stenosis/obstruction found that IVUS was more sensitive and accurate than venography.<sup>102</sup> In the case of nutcracker syndrome, IVUS can clearly show the compression of the left renal vein between the aorta and superior mesenteric artery (SMA)

- thus aiding in the diagnosis (Fig. 32.10) (Video 32.5). In addition, IVUS has been recommended to provide precise vessel sizing intraoperatively.<sup>103</sup> In 1994, a study examining the use of IVUS in the treatment of thoracic outlet syndrome found that IVUS was able to limit the extent of dissection necessary by providing real-time imaging of the release of extrinsic compression.<sup>104</sup> Several more recent studies of patients with thoracic outlet syndrome found that IVUS was able to provide a more detailed evaluation of the subclavian vein than venography, allowing for better identification of high-grade stenosis (Video 32.6).<sup>105,106</sup> In addition, IVUS can help with the diagnosis of TOS when the diagnosis is not straightforward. Although not reported upon, IVUS can help with the diagnosis of other rare presentations such as pectoralis minor syndrome (Video 32.7). Overall, the precise imaging provided by IVUS recommends its use in venous compression syndromes.

## LIMITATIONS AND RISKS

### Comparison of Intravascular Ultrasound with Other Imaging Modalities

Intraoperative imaging options are limited. Although CTA and MRI provide high-quality imaging, they are not usable



**Figure 32.10** Intravascular ultrasound demonstrates the compression of the left renal vein (blue line) between the aorta and the superior mesenteric artery.

during a procedure. Imaging modalities besides IVUS that may be used intraoperatively include intravenous magnetic resonance imaging (IV MRI), optical coherence tomography (OCT), transesophageal echocardiography (TEE), near infrared spectroscopy (NIRS), angiography, and fractional flow reserve (FFR). Compared with other intraoperative imaging

**Video 32.5** Nutcracker syndrome. IVUS pullback from the left renal vein to the inferior vena cava clearly shows the compression of the left renal vein by the superior mesenteric artery. Fluoroscopy clip running simultaneously to show the exact location of the compression.

**Video 32.6** (A) Thoracic outlet syndrome (TOS). IVUS showing compression of left subclavian vein with head rotation to contralateral side. (B) Thoracic outlet syndrome (TOS). IVUS showing compression of left subclavian vein with arm rotation above head level.

**Video 32.7** (A) Pectoralis minor syndrome. IVUS showing axillary vein compression with gentle finger pressure on delto-pectoral groove. (B) Pectoralis minor syndrome. IVUS showing axillary vein compression with shoulder extension.

modalities, IVUS has clear benefits in some cases, while other modalities may be more suited for providing other types of information.<sup>107</sup>

Although angiography and venography are useful in that they provide details of blood flow and vessel contour, allowing visualization of collateral circulation and quality of flow, they are limited in that they do not allow characterization of wall disease and cannot accurately describe size or composition of lesions.<sup>108</sup> Similarly, FFR provides meaningful information about hemodynamic measures of lesion severity but cannot provide information about plaque composition.<sup>109</sup> It was found that in comparing IVUS with angiography for the evaluation and treatment of peripheral arterial disease, IVUS was superior in measuring diameter, areas of stenosis, plaque concentricity, plaque morphology, and calcification.<sup>110</sup> In terms of identifying plaque morphology, IV MRI is also able to characterize the composition of lesions and has been shown to be accurate in measuring vessel wall area.<sup>111</sup> However, although there have been significant improvements to decrease scan time and improve resolution, the associated cost, scan time, and presence of significant movement artifacts has thus far limited the effectiveness of IV MRI.<sup>112,113</sup> Many studies evaluating the efficacy of OCT have found that it is accurate and beneficial in characterizing plaque components in small arteries, such as coronary and infrapopliteal arteries, since it has significantly better spatial resolution than other intraoperative imaging modalities.<sup>114</sup> However, OCT's lack of penetrative depth, small field of view, use of contrast, and the fact that it requires blood removal from the vessel at the time of imaging diminish its usefulness with increased vessel size.<sup>115–117</sup> Overall, its ease of use and increased depth of penetration recommend IVUS for measurements and lesion identification in aortic and peripheral treatments.

## Limitations and Risks of Intravascular Ultrasound

Although the risks associated with the use of IVUS are minimal, IVUS does require an invasive procedure and thus carries the risk of bleeding or clotting in the area of catheter insertion and possible damage to blood vessels. However, since IVUS is often performed in conjunction with other invasive procedures, its use adds little additional risk. Major complications are reported to occur in less than 0.5% of procedures and usually occur during surgical intervention rather than diagnostic imaging.<sup>118</sup> Similarly, the use of IVUS does add additional cost to a procedure, with basic system implementation costing between \$70,000 to \$120,000 and an additional cost per patient of around \$600 for a disposable catheter tip.<sup>119</sup> However, studies of the long-term clinical outcomes of IVUS use suggest that the decreased number of postoperative complications and reduced need for reintervention may offset these costs.<sup>120–122</sup>

Another limitation of IVUS is the quality of imaging. A 2014 study of IVUS, OCT, and IV MRI compared the three imaging modalities and found a comparatively lower quality of imaging with IVUS, with low signal-to-noise ratios and

significant artifacts and interference.<sup>123</sup> Normal ultrasound systems have frame rates between 50 and 750 frames per second, whereas current IVUS systems run at about 30 frames per second, accounting for the difference in image quality, a common complaint of vascular physicians using IVUS. The quality and utility of IVUS images is also user-dependent. Appropriate catheter and frequency selection is key, but other system settings such as gain, compression and rejection (specific to certain mechanical scanners), time-averaging and persistence, and gamma curves must also be adjusted properly to reduce image artifacts and decrease noise while ensuring that targets are not blurred or obscured and that inaccurate measurements are not introduced.<sup>124</sup> Physicians utilizing IVUS must recognize potential pitfalls in interpreting images, being aware of near-field and motion artifacts as well as artifacts created by transducer position, taking into account catheter obliquity and vessel curvature as well as angle-dependent artifacts that may be created by catheter eccentricity.<sup>125,126</sup> Technician support should be available and standards, protocols, and education should be established to ensure that IVUS use is as effective and efficient as possible.

## FUTURE ADVANCES

In the future, technological advances may overcome some of the limitations of IVUS, allowing for improved imaging and ease of use. Currently, IVUS creates images with axial slices at 90 degrees to the probe, which limits its usefulness in guiding wires through chronic total occlusions. Recent advances in technology to overcome this limitation include the development of a single-chip forward-looking imaging system created by integrating capacitive micromachined ultrasonic transducer (CMUT) arrays with front-end electronics.<sup>127–129</sup> This type of array may also allow for IVUS use on guidewires, thus simplifying procedures by eliminating the need for separate catheters.<sup>130,131</sup> Identification and characterization of plaques with IVUS may also be improving. The PROSPECT II trial is currently under way to evaluate the efficacy of a cardiac catheter combining IVUS with NIRS to help identify and characterize vulnerable lipid-rich coronary plaques.<sup>132</sup> NIRS has been shown to be more accurate than IVUS in characterizing soft plaques, so its combination with IVUS contributes to the accurate characterization of vulnerable plaques by providing precise information about lesion morphology.<sup>133–135</sup> Combination technologies, such as systems that integrate FFR or NIRS with IVUS, along with other types of technology that integrate IVUS with treatments such as angioplasty or ablation, may be the most promising developments for IVUS in the years ahead.<sup>136</sup>

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# The Future of Imaging for Endovascular and Open Surgery

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## BACKGROUND

Vascular surgery has pioneered the development of various novel, minimally invasive catheter-based endovascular procedures within the confines of the open surgical operating room (OR). Portable image intensifier-based C-arm systems were the original imaging platforms on which catheter-based therapies have evolved in the hands of vascular surgeons. Thus far, the portable C-arm imaging system has been the signature imaging tool in the OR that heralded the entry of open vascular surgeons into the endovascular interventional space. With the advent and rapid evolution of imaging technologies in the OR, vascular surgeons are now required to have an increased understanding of both basic and advanced imaging techniques.

As the reach and complexity of endovascular therapies have evolved with advancements in endovascular devices such as steerable catheters, novel conformable stents, and stent grafts with custom-made branches or fenestrations, imaging technologies have also evolved in parallel. Image intensifiers in the portable C-arm imaging systems have been replaced with flat

panel-based digital image detector systems and provide better image quality, signal-to-noise ratio, and dynamic range with little to no geometric distortions.<sup>1</sup> However, the portable nature of these C-arm systems is still a limitation for having a more powerful X-ray tube with better cooling capabilities. Because of the advanced imaging demands for longer and more complex vascular procedures, fixed angiography imaging suites, traditionally the province of interventional cardiologists and interventional radiologists, have become commonplace within the OR environment. Often referred to as hybrid rooms, they allow for both “open” surgical procedures and catheter-based endovascular interventions to be optimally performed in the same operating suite. Although expensive, hybrid ORs, for the very first time, have paved the way for intraoperative cone-beam CT imaging and preoperative 3D image fusion guidance in the hybrid OR.<sup>2-4</sup> This has been followed by technologies such as flexible endovascular robotics and the integration of multiple imaging modalities including transesophageal echocardiographic imaging (TEE), intravascular ultrasound (IVUS), intracardiac echocardiography (ICE), preoperative

computed tomography (CT), and magnetic resonance imaging (MRI) within the hybrid OR.

Indeed, the rapid evolution of imaging and endovascular devices is symbiotic and synergistic. Despite the evolution of intraoperative advanced imaging capabilities, there has been an increasing concern about the long-term effects of occupational radiation exposure to the surgical team and ergonomics of radiation protection gear. Consequently, newer methods are evolving for real-time monitoring of radiation exposure and minimizing the amount of radiation employed during these procedures.

The goal of this chapter is to impart a broad overview of the recent evolution of advanced X-ray and multimodal imaging techniques for vascular surgery interventions and to provide a glimpse into potential future imaging and catheter navigation technologies that could improve the safety and efficacy of endovascular procedures while minimizing the amount of radiation exposure to the patient and healthcare team in the hybrid OR.

## X-RAY IMAGING AND HYBRID OPERATING ROOMS

Although alternate radiation-free imaging modalities such as ultrasound and MRI are available and less invasive, diagnostic imaging for endovascular interventional and surgical procedures has primarily been superseded by multi-slice conventional CT imaging, invasive 2D X-ray fluoroscopy and angiography. Despite being a 2D projection imaging technique, the primary advantage of 2D X-ray angiography is considered better with spatial resolution of around 0.2 mm in imaging smaller vessels with temporal resolution of ~20 ms after injecting a bolus of an iodinated contrast agent into the vessel of interest.<sup>5</sup>

### Portable C-Arm Imaging Systems

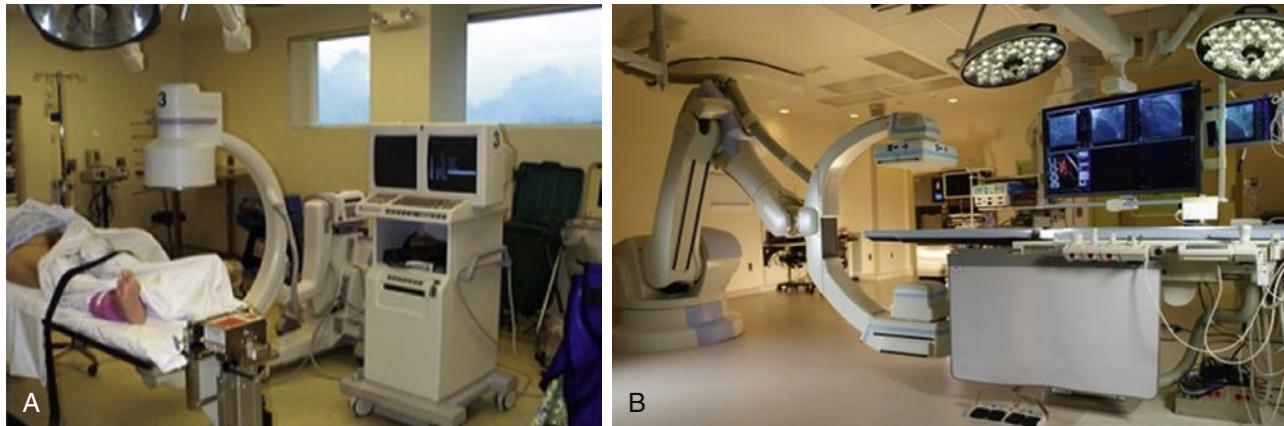
Although the portable image intensifier-based C-arm imaging system has been the staple imaging modality for vascular surgery for many years, it has continued to evolve with technological advancements. For example, the image intensifier-based

X-ray detector system has been replaced by the flat panel-based digital detectors; these have better sensitivity and lower noise levels, potentially offering better distortion-free image quality at a lower radiation dose.<sup>1</sup> In addition, newer X-ray tubes in mobile C-arms with higher power generators – in the order of 25 kW – and better cooling capabilities enable higher penetration power even in obese patients. Moreover, these allow uninterrupted imaging for longer endovascular procedures than was possible with fixed C-arm angiographic imaging systems.<sup>6,7</sup> Radiation exposure to both patients and the surgery team needs to be carefully considered during the usage of mobile C-arm imaging systems in the OR.<sup>7,8</sup> Perhaps the most revolutionary development is 3D imaging in upcoming mobile C-arm imaging systems. Although there has been some preliminary work using this 3D imaging technique during bronchoscopic and orthopedic procedures,<sup>4,9,10</sup> routine clinical use of this technology for vascular imaging is still evolving.

Recent advancements in mobile C-arm imaging systems, including image fusion and overlay capabilities, are very relevant. In most vascular surgery practices, the portable low-end mobile C-arm imaging system continues to be the primary imaging modality or a backup imaging option to the fixed hybrid OR. Moreover, portable C-arm imaging-based interventional suites have been increasingly used to set up office-based vascular practices (Fig. 33.1). With the technological gap between portable and fixed C-arm imaging systems narrowing, mobile C-arms could represent a very practical and economical option for an outpatient interventional or endovascular suite, permitting both the technical and professional revenues to be captured in an office-based vascular surgery practice.

### Fixed C-Arm Angiographic Imaging Systems

Typically the concept of a hybrid OR is one where high-resolution angiography can be performed in the same room – even concomitantly – as complex open surgical procedures. Over time, the concept of hybrid OR has been generalized, and not all hybrid ORs are equal. In this context, a modern, high-end hybrid OR often references one that is equipped with a fixed C-arm imaging system that can enable open, endovascular, or hybrid minimally invasive surgical procedures. A typical fixed



**Figure 33.1** (A) Standard low-end mobile C-arm. (B) Fixed imaging system mounted on a robotic arm.

C-arm angiographic imaging system can be floor- or ceiling-mounted and is integrated to the OR table, with the option of surgical tables to improve the utilization of the hybrid suite across various surgical specialties.<sup>11</sup> In addition, fixed C-arm angiographic imaging systems mounted on a robotic arm offer versatility and the option of bringing the imaging system to the patient whenever needed during the surgical procedure (see Fig. 33.1).<sup>12</sup>

### **Concept of “As Low As Reasonably Achievable” and “Low”-Dose Radiation to the Patient**

Monitoring radiation dose delivered to the patient and training and awareness of radiation safety for the entire OR team is critical but often overlooked. Adherence to ALARA (As Low As Reasonably Achievable) strategies should be a key part of training and must not be seen as a matter of convenience. However, in a recent anonymous survey of vascular surgery trainees, 45% had no formal training in radiation safety and 43% were unaware of annual maximum acceptable levels of radiation exposure.<sup>13</sup> In the same study, the vascular trainees also perceived themselves as practicing ALARA strategies, when they perceive that their attending physicians are regularly practicing ALARA strategies.<sup>13,14</sup> This further highlights the value and immediate need for improvement in radiation safety measures to optimize the radiation dose delivered to both patient and the operating team.<sup>15–20</sup>

### **Protection from Radiation Scatter**

One of the challenges associated with radiation safety education is that the training is based on non-intuitive understanding of radiation scatter patterns in the OR. However, in certain scenarios, stepping away from the patient to respect inverse square law is not always feasible. The scenarios related to radiation safety must be redefined from an OR perspective. Recent studies have attempted to map radiation scatter patterns in the OR using personal wireless dosimeters,<sup>21–23</sup> which would pave a great step into the future of radiation safety training measures.

### **Designing a Hybrid Operating Suite**

When designing a high-end hybrid OR, it is very important to consider the following factors: (1) type of procedures that will be performed in the room; (2) adequate area and ceiling height of the room; (3) location and proximity to other ORs or pre-existing interventional suites and intensive care units; (4) recruiting experienced specialist architects, local hospital planning, and construction team; (5) involvement of all primary users and surgical and anesthesia departments throughout planning and execution process; (6) including strategic vendors; (7) determining appropriate staffing with dedicated OR managers, nurses, X-ray technologists, and a backup team; and more importantly, (8) adequate communication, education, and training of the entire OR team. Building a hybrid OR service typically takes a few months to years from design to construction and being fully operational. It involves cohesive interaction between various clinical disciplines working together

with specialist architects, imaging equipment vendors, OR equipment vendors, and hospital biomedical engineers. Therefore detailed planning that takes into consideration ergonomics, clinical workflow, integration of imaging and informatics, and adequate risk management strategies is paramount. After all, these are some of the most expensive ORs built in the hospital and require careful planning and execution.<sup>11,24,25</sup>

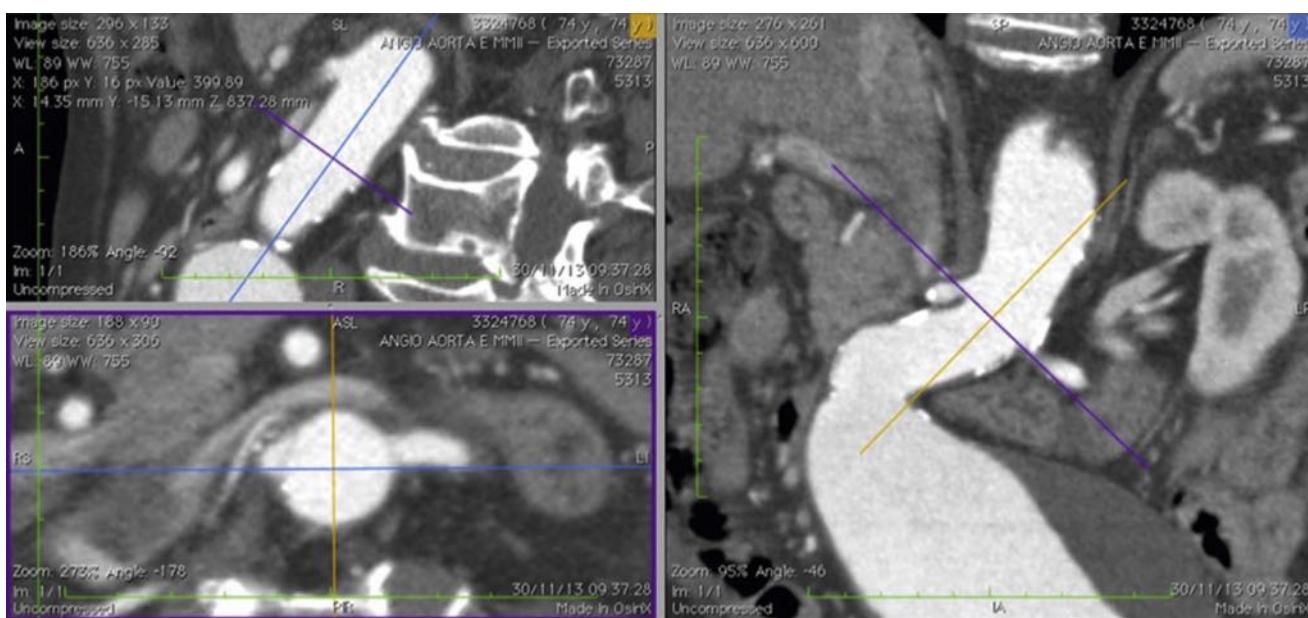
Although installation of the imaging system may often seem like the most important decision, it is not the main challenge. Configuring and installing all the other OR accessories including overhead lights and booms, anesthesia equipment, imaging equipment, and cardiopulmonary bypass pumps all require careful planning and workflow considerations. Adequate staffing and training is another major often overlooked factor in the final functioning of a hybrid OR. Dedicated, highly trained interventional technologists and OR nurses familiar with both X-ray and multimodality 3D imaging are essential. It is also important to train some of the technologists to act as “special procedure” technologists and nurses to ensure adequate exposure and to maintain experience and skills training. In summary, tight integration of patient scheduling, audio, video, imaging, patient monitoring, and hospital informatics systems in a hybrid OR should enable seamless display and access to all the preoperative, intraoperative, and postoperative information during the surgical interventions.

## **ADVANCED 3D IMAGING AND IMAGE GUIDANCE TECHNIQUES**

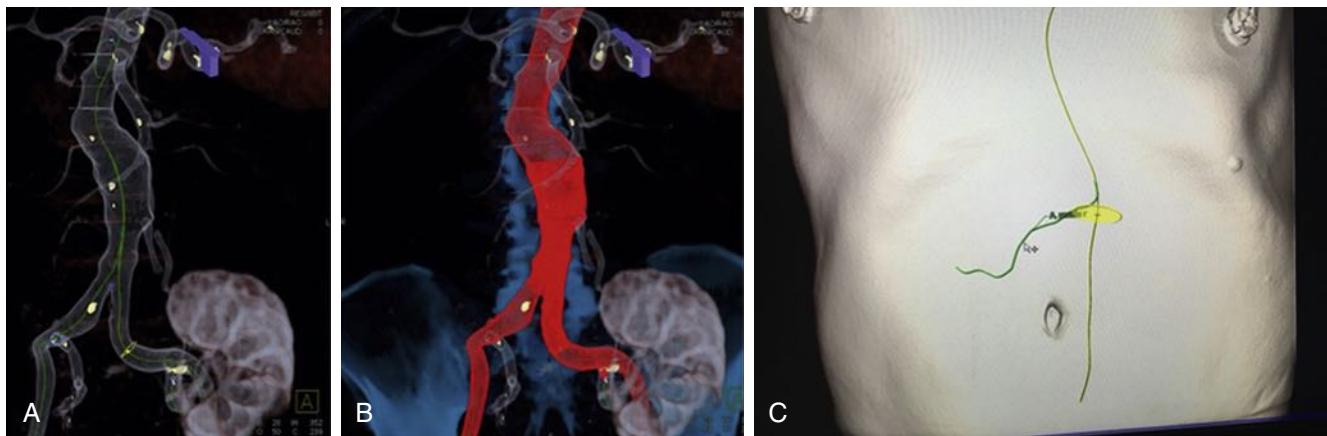
### **Preoperative Imaging and Why this Impacts Procedural Performance**

Until recently, preoperative CT or MRI scans were used as tools for diagnosis and decision making. However, for presurgical planning, a surgeon needs to review the images in multiplanar (Fig. 33.2), volume-rendered reconstructions (Fig. 33.3) and plan the endovascular or open surgical intervention. The evolution of endovascular stent grafting spurred parallel development of third-party, post-processing software packages that facilitate advanced image visualization techniques, including multiplanar reconstructions, and now even provide advanced virtual stent graft planning software.

The latest generation of hybrid ORs has evolved with advanced imaging techniques such as acquiring three-dimensional cone-beam CT imaging, and advanced image fusion techniques such as 3D–3D image fusion and 2D–3D image fusion to incorporate preoperative imaging data. Consequently, the technique and quality of preoperative imaging is increasingly important not just for diagnosis but also for intraoperative use. This should be kept in mind during acquisition of preoperative images using CT and MRI protocols that generate high-resolution, thin-slice acquisitions that facilitate accurate 3D rendering and image fusion techniques. For example, during imaging for type II endoleak evaluation, acquiring high-resolution 3D datasets encompassing both arterial and delayed phase enables the surgeon to understand and target the inflow and outflow



**Figure 33.2** Multiplanar views of computed tomographic angiography (CTA) allowing for interventional planning.



**Figure 33.3** (A,B) Volume-rendered reconstructions of computed tomographic angiography (CTA); (C) Surface rendering of CT scan.

patterns within the endoleak-feeding vessels. Once endovascular targets are defined on the preoperative CT images, these same targets can be overlaid onto the fluoroscopic image to guide interventions such as selective embolization.<sup>26–28</sup> In the long run, this will optimize judicious usage of radiation and contrast agents in patients during diagnosis and interventions.

Even when an open surgical procedure is planned, surface rendering of a CT scan will show the surface features of the patient such as prior surgical scars, nipples, and umbilicus (Fig. 33.3C). This can be directly used for surgical incision planning after a surface-to-surface image co-registration process.<sup>29</sup> Understanding how to interact with the 3D imaging datasets can transform endovascular procedural planning and optimize incision planning and targeted approaches for minimally invasive open surgical procedures.

In summary, preoperative imaging and planning helps with achieving appropriate device sizing, avoiding parallax by selecting optimal C-arm angulation and providing a 3D roadmap during interventions after image fusion. Finally, the cardiovascular system is highly dynamic: the aorta varies in diameter and

position with cardiac and respiratory cycle, the inferior vena cava (IVC) varies in diameter with respiration, and the aortic dissection septum moves extensively during systole and diastole. The emerging role of dynamic multimodality imaging such as CT and MRI in understanding the cardiovascular system is undisputable.<sup>30,31</sup> Increasingly, these dynamic images are being incorporated into both diagnosis and interventional procedure guidance, such as endovascular stent grafting for complex aneurysms and dissections of aortic arch and ascending aorta.

### C-Arm Cone-Beam Computed Tomography Imaging

In addition to 2D X-ray fluoroscopy and angiography, recent fixed C-arm angiographic imaging systems provide the additional capability of intraoperative 3D imaging by acquiring a series of 2D projections while the C-arm rotates around the patient for 200 degrees and reconstructing them as 3D cone-beam CT images. The development of high-contrast 3D angiographic imaging within the interventional neuro-radiology

suites, and more recently, 3D cone-beam CT imaging capabilities, have revolutionized minimally invasive catheter-based interventions.<sup>28,32–34</sup> This cone-beam CT imaging technology and associated clinical applications have historically been well adopted and integrated in neuro-interventional and interventional radiology suites. To ensure consistency, the term “CBCT” has been used from here on to refer to intraoperative cone-beam CT imaging technique. Of course, different imaging vendors tend to use their own trademark terms – such as syngo DynaCT (Siemens Healthcare GmbH, Germany) or XperCT (Philips Medical Systems) or InnovaCT (General Electric Medical Systems) – adding to confusion surrounding individual room capabilities and adequate training. However, the penetration of these intraoperative 3D imaging and image fusion techniques into the OR is rather recent and comes with its own challenges and opportunities. Evolution of such 3D imaging modalities in the OR could impact both the conduct of open surgical and endovascular procedures and could support the surgical community’s further development of incremental technologies such as flexible-catheter robotics. Consequently, CBCT is a very versatile intraoperative imaging tool that can be considered the gateway for application of very sophisticated CT imaging applications in the future.<sup>2,11,28,35,36</sup> Along with this heavy dependence on X-ray imaging, however, there is an increasing concern about the amount of radiation exposure for surgeons and OR personnel.<sup>19,37</sup> Consequently, newer methods have been developed for monitoring radiation exposure and minimizing the amount of radiation delivered to the patient and surgical team during these procedures.<sup>38,39</sup> Nevertheless, the potential complementary role of other radiation-free tracking or imaging techniques, such as optical or electromagnetic device tracking and ultrasound and MRI, needs to be explored, especially for complex open and endovascular surgical procedures.

## CT Image Fusion and Guidance Techniques

While having access to a fixed hybrid OR with its multiple advanced imaging capabilities is necessary for the conduct of complex endovascular procedures, the ability to perform a CT in the OR represents the next huge technological leap for vascular surgeons. It allows them to understand the intraoperative status of vasculature and stent grafts immediately after deployment to rule out potential endoleaks, kinking, and bird-beaking of stents, thus potentially avoiding a future reintervention.

However, the core functionality of such an intraoperative imaging system is the ability to create a 3D DICOM dataset in the hybrid room. Until the real CT imaging capability in the OR is adopted into routine, image fusion of preoperative datasets can be performed using 2D–3D and 3D–3D image fusion techniques.<sup>20,40,41</sup> This minimizes additional radiation, avoids giving additional iodinated contrast usage, and allows the operator to use the entire prior computed tomographic angiography (CTA) dataset, which is often much more extensive than that which can be obtained using CBCT.

3D–3D image fusion technique involves co-registration of a noncontrast CBCT dataset with a preoperative CT or MR

dataset. After image fusion, the structures of interest electronically annotated in the preoperative dataset can be overlaid on the fluoroscopic image during intervention.<sup>36,42,43</sup> The significant advantage of this 3D–3D image fusion is that relevant structures can be matched between two 3D datasets and no additional angiographic contrast is necessary during intervention. Additional non-radiation imaging such as IVUS or low-dose carbon-dioxide (CO<sub>2</sub>) angiography can be used to verify and complement 3D–3D fusion imaging. Furthermore, automated image segmentation algorithms can extract relevant vascular landmarks such as aortic centerlines, renal artery, and internal iliac artery ostia and overlay them onto fluoroscopy (Fig. 33.3A,B). To demonstrate this image fusion process, we describe our workflow for endovascular abdominal aortic aneurysm repair (EVAR) using endografts. First, the patient is typically evaluated using outpatient thin-cut multi-slice CTA (MSCT). Next, after the patient arrives in the hybrid OR and is prepped and draped, a low-dose noncontrast CBCT is typically performed. A 3D postprocessing workstation was used to fuse noncontrast CBCT with the preoperative MSCT. An automated image segmentation algorithm then segments the vascular structures and relevant landmarks consisting of the aorta and its major branches. Then, after image fusion, all the relevant vascular structures segmented are immediately overlaid on the live fluoroscopy, even before the first injection of contrast agent during the procedure. Image fusion is typically achieved by aligning and fusing bony structures between CBCT and MSCT datasets. In theory, if the ribs, vertebrae, and pelvis are aligned, then the vascular structures should also be aligned. Bony structures are used to perform fusion because they are easily visible on noncontrast CBCT. However, there are a few limitations: if the patient is positioned differently during preoperative imaging and during the intervention, aligning bony landmarks may not achieve accurate alignment of vascular structures. Typically patients’ arms are positioned abducted above their heads during preoperative CT imaging and are positioned adducted by their sides in the OR. Therefore dedicated context-specific image fusion techniques based upon vascular wall calcifications have been developed.<sup>41,44,45</sup> The vascular wall calcifications can be thought of as the bones of the blood vessels. This technique is possible and reliable because most of our elderly EVAR patients have extensive calcification easily visible on MSCT and CBCT. Based on our preliminary experience, we have found this to be a highly accurate method for fusing vascular structures.<sup>44</sup>

Another recently available image fusion technique can co-register preoperative images to fluoroscopy without the need for acquiring noncontrast CBCT imaging. This 2D–3D image fusion technique works by acquiring two fluoroscopic images acquired at least 30 degrees apart and fusing them with digitally reconstructed radiographs derived from preoperative 3D images.<sup>40,46</sup> Although this 2D–3D image fusion simplifies the image fusion workflow, the accuracy of this technique needs to be further validated.<sup>47</sup> In the future, it is likely that the image fusion technique will be preferred based upon the clinical context and accuracy necessary for conducting the procedure safely. For the time being, until robust automated workflow-specific

algorithms are routinely available, injection of dilute contrast agent or CO<sub>2</sub> angiography is typically performed to confirm image fusion accuracy before device deployment.

## MR Image Fusion and Guidance Techniques

Various studies have reported the incremental value of image fusion during endovascular aortic procedures with a significant reduction of procedure length, radiation dose, and injected contrast agent volumes.<sup>48–53</sup> Because of the high risk of acute tubular necrosis, CTA with iodinated contrast injection is contraindicated in patients with severe renal insufficiency (glomerular filtration rate (GFR) <30 mL/min/1.73 m<sup>2</sup>) and should be avoided in those with moderate renal insufficiency (GFR between 30 and 60 mL/min/1.73 m<sup>2</sup>).<sup>54</sup> One of the main advantages of image fusion techniques is reduction in the use of iodinated contrast agents in these patients with renal insufficiency. Contrast-enhanced magnetic resonance (MR) angiography (MRA) is an alternative imaging technique to CTA and is performed safely, even in patients with end-stage renal disease, using an iron-based contrast agent, ferumoxytol (Feraheme; AMAG Pharmaceuticals, Waltham, MA).<sup>55,56</sup> Such MRA images acquired in 3D format could be used as a preoperative imaging data set for further intraoperative image fusion guidance.

Our MR protocol is derived from standard, preset, readily available protocols from the MR imaging (MRI) scanner vendor, with slight modification. In patients without renal insufficiency, gadopentetate dimeglumine (Magnevist; Bayer Healthcare, Whipppany, NJ) is used to provide blood contrast at a concentration of 0.2 mL/kg. In patients with renal insufficiency, end-stage renal disease or acute kidney disease, infusion of 90 mg of ferumoxytol (Feraheme), diluted in a 1:8 ratio with saline was used (after exclusion of iron overload by laboratory testing and MRI assessment of liver using cardiac T2 imaging) to enhance vascular delineation.

Arterial and venous phase first-pass MRA imaging is performed using a 3D gradient echo sequence. In addition, ~10 minutes after contrast administration, an equilibrium phase, fat saturated, volumetric interpolated breath-hold examination (VIBE) 3D gradient echo sequence is performed. The VIBE sequence also allows for better delineation of bony landmarks that could be leveraged for intraoperative image fusion.

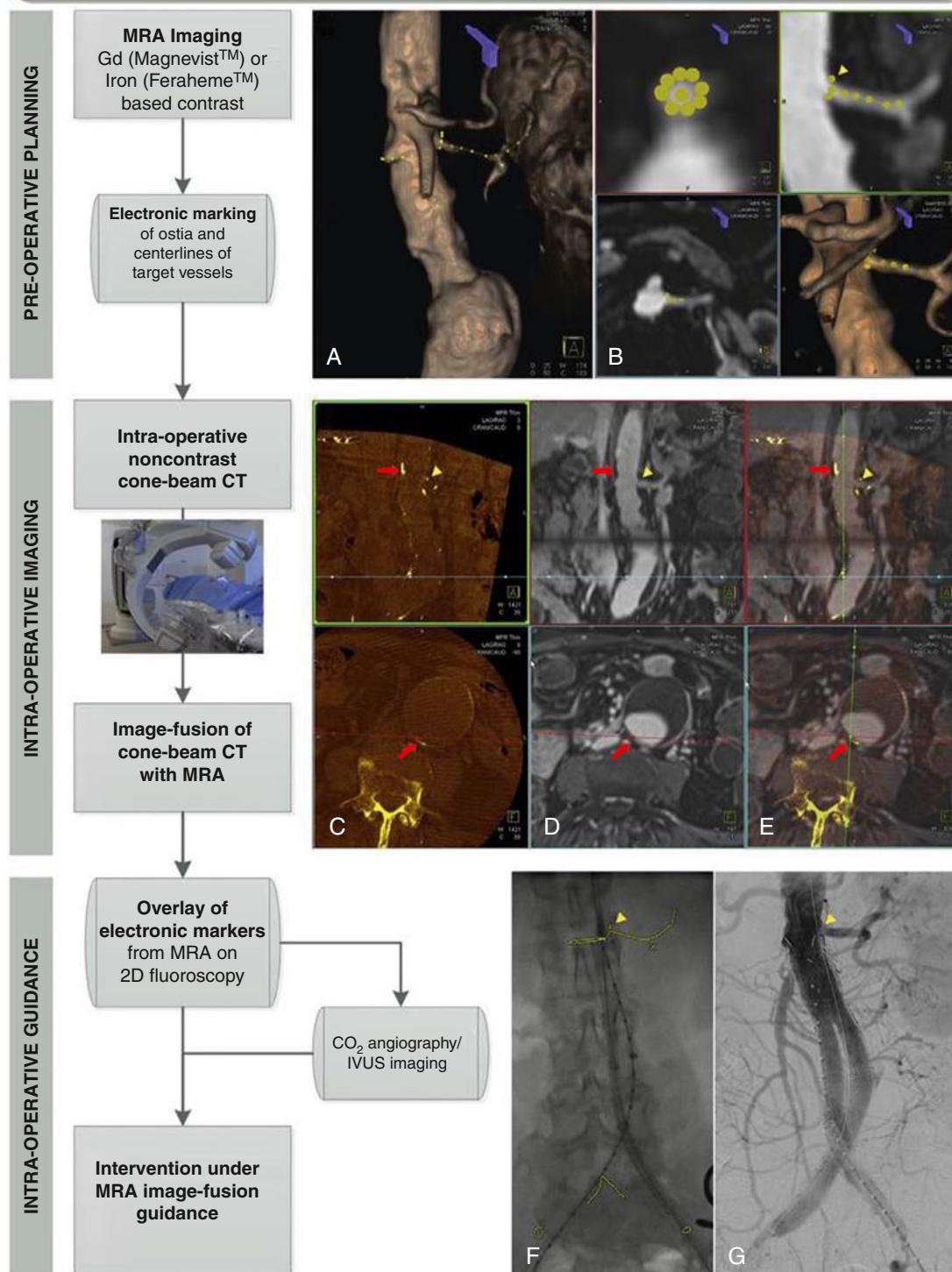
Similar to image fusion techniques for multi-slice CTA, preoperative MRA images are imported from the picture archiving and communication system into the 3D workstation in the operating room and reconstructed in multiplanar reconstruction and 3D volume-rendered formats. Under general anesthesia and breath-hold, an intraoperative noncontrast CBCT is acquired in the hybrid operating room. 2D projection X-ray images acquired over 200-degree C-arm rotation around the patient are reconstructed as CBCT images using dedicated reconstruction algorithms in the 3D workstation. Noncontrast CBCT images are then co-registered with MRA images using a dedicated software application (*syngo Inspase 3D-3D fusion*, Siemens Healthcare), followed by appropriate manual refinements using landmarks pertinent to the individual procedure,

such as vessel contours, calcifications, indwelling stents and catheters. This process is somewhat more labor intensive and has a more significant learning curve, than when CTA images are used as the reference imaging. As such there is, at times, a need to perform a single contrast-enhanced image using iodinated contrast agent or CO<sub>2</sub> to use as an additional frame of reference.

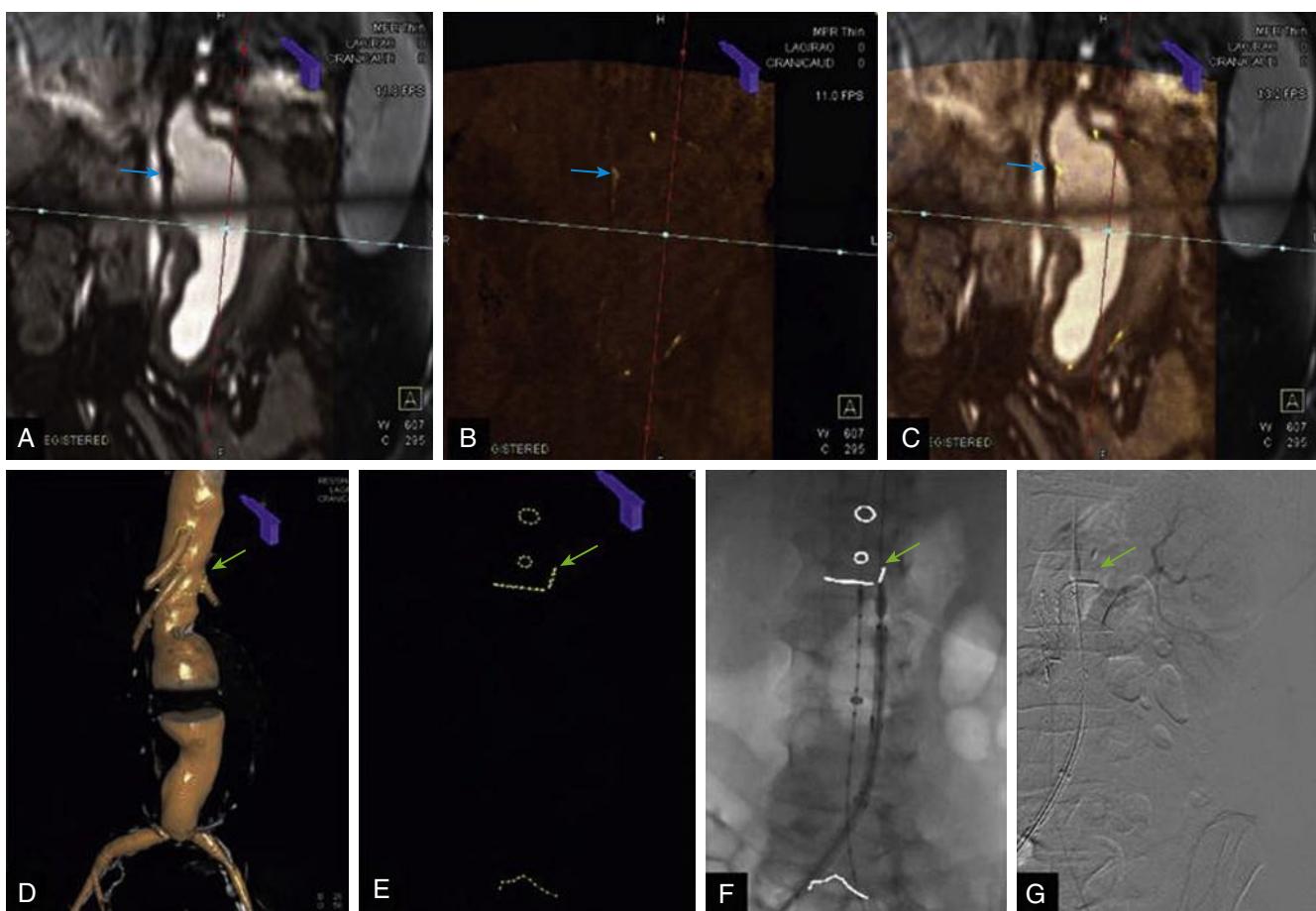
After MRA-CBCT image co-registration, landmarks such as the ostium or centerline of targeted vessels as well as proximal or distal optimal stent graft landing zones, are electronically marked on the MRA images using a dedicated application. These electronically marked landmarks are then projected in real time onto the live intraoperative fluoroscopic images during arterial cannulation and stent graft deployment. In other words, these landmarks from MRA images overlaid on fluoroscopy are updated in real time with changes in C-arm angulations, table movements, and image zoom (Fig. 33.4). Feasibility of 3D MRA–fluoroscopy image fusion technique in guiding complex endovascular aortic procedures in patients with renal insufficiency was shown in our study (Fig. 33.5). Schwein et al. showed the feasibility and value of these imaging techniques, importantly demonstrating no change between pre-imaging and postoperative renal function ( $P = 0.6$ ).<sup>42</sup>

Magnetic resonance venography (MRV) has been demonstrated as an emerging modality for imaging and characterizing venous occlusive disease with excellent repeatability, such as characterization of thrombus in deep venous vasculature and measurement of thrombus age.<sup>55,57</sup> In addition, time-resolved MR venography has been shown to be helpful in central venous access in challenging patients.<sup>58</sup> These studies highlight the novel information that MR imaging reveals not only from a diagnostic perspective but also from an interventional perspective. To minimize nephrotoxicity in patients with chronic renal failure, MR imaging of central veins using noncontrast techniques such as time-of-flight MRA sequence and 3D steady-state free-precession sequences have been developed.<sup>59</sup> As described above, in these patients, Feraheme may be used to provide blood pool imaging that is often well-suited for imaging central and peripheral venous disease.<sup>56,60</sup> More recently, respiratory gated noncontrast SPACE MRA sequence has been shown to image central veins with better signal- and contrast-to-noise ratios.<sup>61</sup> In addition, recent MR imaging techniques such as compressed sensing and parallel imaging have enabled faster image acquisition time while maintaining data consistency. Such advances will enable contrast agent free, flow-independent imaging and help bring the power of MR imaging into clinical routine.<sup>62,63</sup>

The underlying hypothesis behind MRV imaging for central venous occlusions is that, in addition to mapping the occluded venous segments, delayed imaging with a blood-pool contrast agent may be able to visualize perivascular structures such as the vasa vasorum of chronically occluded veins. From an interventional standpoint, this key information may help when occluded venous segments are not well visualized by luminal angiography. MR imaging has the potential to integrate vessel wall information, such as outline of vasa vasorum from originally occluded veins, obtained by fluoroscopy, for example,

**MRA Image Fusion Technique for Aortic Interventions in Patients with Renal Insufficiency**


**Figure 33.4** Detailed workflow illustrates the magnetic resonance angiography (MRA)–fluoroscopy image fusion technique using noncontrast cone-beam computed tomography (CT; CBCT) for aortoiliac interventions in patients with renal insufficiency. Gd, gadolinium. **(A,B)** Preoperative planning involves two-dimensional (2D) and three-dimensional (3D) post-processing of MRA datasets and electronic marking of vessel ostia, for example, for left renal artery (yellow arrowhead), centerlines and other relevant landmarks (planned landing zones, aortic bifurcation). Intraoperative imaging involves **(C)** 5-second noncontrast CBCT image acquisition under breath-hold and **(D)** coregistration with the preprocedural MRA dataset. **(E)** The image fusion process is automatically initialized based on bony anatomy and manually refined based on alignment of aortic contours and calcifications (red arrow). **(F)** Overlay of vessel ostia and landmarks on fluoroscopy and **(G)** completion angiogram after stent graft deployment are shown. CO<sub>2</sub> angiography or intravascular ultrasound (IVUS) imaging techniques were used in conjunction, if indicated.

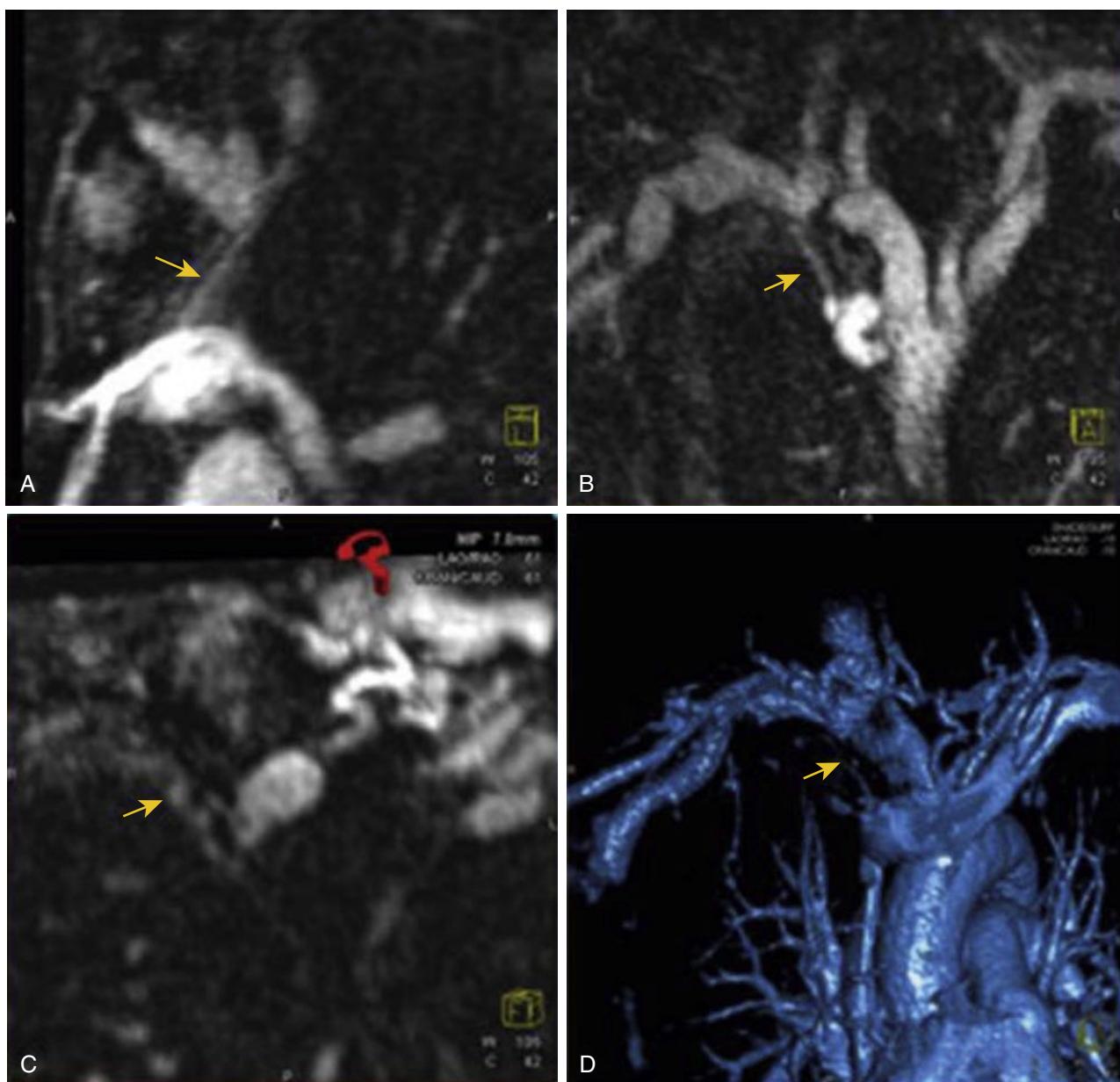


**Figure 33.5** A 68-year-old woman with an intrarenal aneurysm was referred for endovascular aneurysm repair (EVAR). She had a solitary left kidney, a preprocedural serum creatinine of 1.6 mg/dL, and a glomerular filtration rate (GFR) of 32 mL/min/1.73 m<sup>2</sup>. (A–C) Coronal reconstruction of a T1-volumetric interpolated breath-hold examination (VIBE) magnetic resonance image (MRI) after Feraheme contrast injection (AMAG Pharmaceuticals, Waltham, MA), noncontrast cone-beam computed tomography (CBCT), and fused image shows accurate alignment of the aortic contours, including wall calcifications (blue arrow), from CBCT with signal void in the MRI after image coregistration. (D) Dual volume reconstruction of magnetic resonance angiography (MRA; in golden preset) and wall calcification from CBCT (in white) with electronic landmarks (green arrow) for celiac, superior mesenteric artery, and left renal ostia, landing zone for the stent graft, and the aortic bifurcation. (E) After image fusion, the landmarks are used to compute ideal C-arm angle for device deployment that minimizes parallax in the left renal ostium with respect to the aortic lumen. This optimal C-arm angle is derived after accounting for differences in intraoperative patient position compared with MRA imaging. (F) Fluoroscopic image with overlaid electronic landmarks, verified by intravascular ultrasound (IVUS) imaging before stent graft deployment. (G) Angiogram after main body of stent graft deployment with 50% dilute contrast agent injected after selective cannulation of the left renal artery.

during endovascular recanalization of chronically occluded central veins (Fig. 33.6). Such complementary information of the occluded venous wall may be integrated as an overlay onto fluoroscopy during complex endovascular recanalization procedures for better 3D guidance. 3D–3D image fusion can be further optimized by aligning the bony landmarks or indwelling catheters/wires in the noncontrast CBCT with central venous vasculature in the MRI dataset.<sup>43</sup> This intraoperative CBCT provides soft-tissue information for troubleshooting in complex cases to better understand 3D catheter orientation relative to the target vessel and to rule out perforation during recanalization attempts. Once image fusion is completed, the electronically annotated vessel landmarks and centerlines can be overlaid onto fluoroscopy during recanalization attempts (Fig. 33.7). These landmarks are automatically tracked with changes

in C-arm positions, image zoom, and table movements. Using an MR fluoroscopy overlay of the target vessel enhances procedural planning and provides additional guidance to better visualize the venous lesions during complex procedures and has been shown to correlate with recanalization success in patients who underwent prior attempts without image fusion. Our own study showed that MR and CBCT imaging parameters, and detailed procedural results suggest that MRV image fusion is feasible and may improve procedural safety and success.<sup>43</sup>

Despite the advantages of information gleaned from multimodality preoperative imaging data in optimizing the C-arm angulation prior to angiography and overlay onto fluoroscopy for guidance during intervention, the obvious limitation is that any prior image dataset does not reflect the changes in vasculature that occur during intervention. The interventionalist still



**Figure 33.6** (A–D) Preoperative magnetic resonance venography shows hypersignal of the boundaries of the occluded right brachiocephalic vein (arrows).

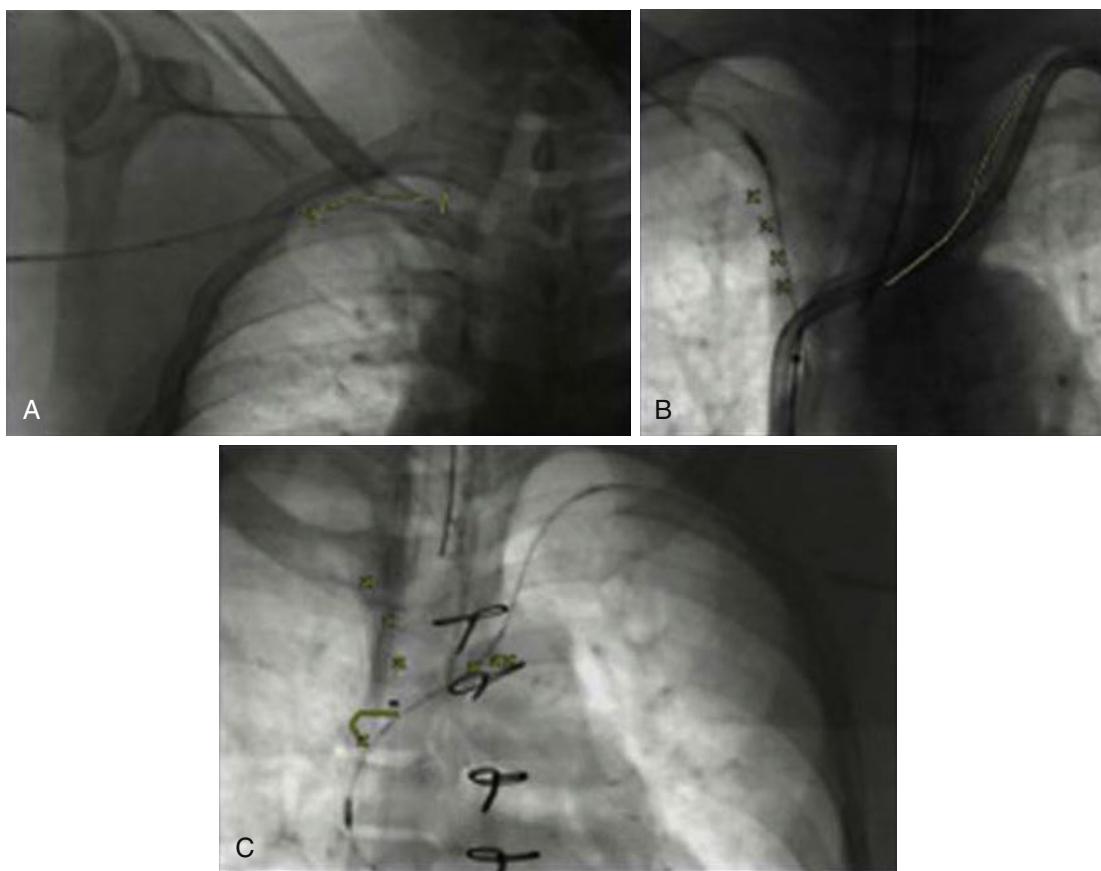
needs to navigate wires and catheters based on limited information. The addition of real-time intravascular ultrasound can be used for further imaging. These images can be co-registered with fluoroscopy or digital subtraction venography during the intervention to compare and understand the lesion morphology and features in both imaging modalities.<sup>64,65</sup> Any additional imaging data acquired during the procedure that can potentially influence interventional decision-making can be integrated into the procedural workflow. In this context, future interventional suites or hybrid operating rooms are poised to gather and incorporate multimodality imaging data into therapeutic decision-making.

In fact, multimodality combination imaging suites and hybrid operating rooms are being installed, where intraoperative MRI or CT imaging can be performed during the surgical

procedure for procedural guidance and confirmation of treatment. Rather than using preoperative CT or MRI datasets to provide procedural guidance, new suites and hybrid operating rooms can provide seamless real-time intraoperative images to assist with procedural guidance, improved safety, and optimizing therapeutic decisions. This highlights the need for an integrated platform for multimodality image acquisition and image guidance during complex vascular interventions.

### Needle Guidance

Not all procedures performed by vascular surgeons are endoluminal and permit target access via the peripheral arterial or venous vasculature. A few examples of needle-based procedures in the vascular surgical suite include percutaneous embolization



**Figure 33.7** (A–C) Completed image fusion with the electronically annotated vessel landmarks and centerlines.

of the aortic aneurysm sac for treatment of type II endoleaks using translumbar or transabdominal approaches.<sup>27,48,66</sup> Conventionally this has been performed using bony landmarks, as seen on fluoroscopy, and carefully avoiding the puncture of the stent graft.

The workflow for 3D needle guidance has been illustrated using CBCT imaging and dedicated needle guidance software offered by most imaging vendors. The ability to perform intraoperative CBCT and fuse with a previously acquired MSCT or MRI in which the endoleak and feeding vessels are delineated is beneficial. Even with the patient placed in the prone position on the hybrid OR table, the stent grafts from two datasets can be aligned to achieve accurate image fusion. The target endoleak site is typically electronically marked in the preoperative CT dataset (arterial or delayed phase). This virtual needle path is electronically marked on the CT dataset and overlaid on 2D fluoroscopy during needle advancement. In addition, the integrated laser crosshairs built in the detector help with guidance of needle entry point in the skin to achieve ideal bull's-eye trajectory to reach the target endoleak site. Availability of virtual needle path overlay in all C-arm angulations helps with accurate 3D guidance and needle progression to the endoleak site (Fig. 33.8).

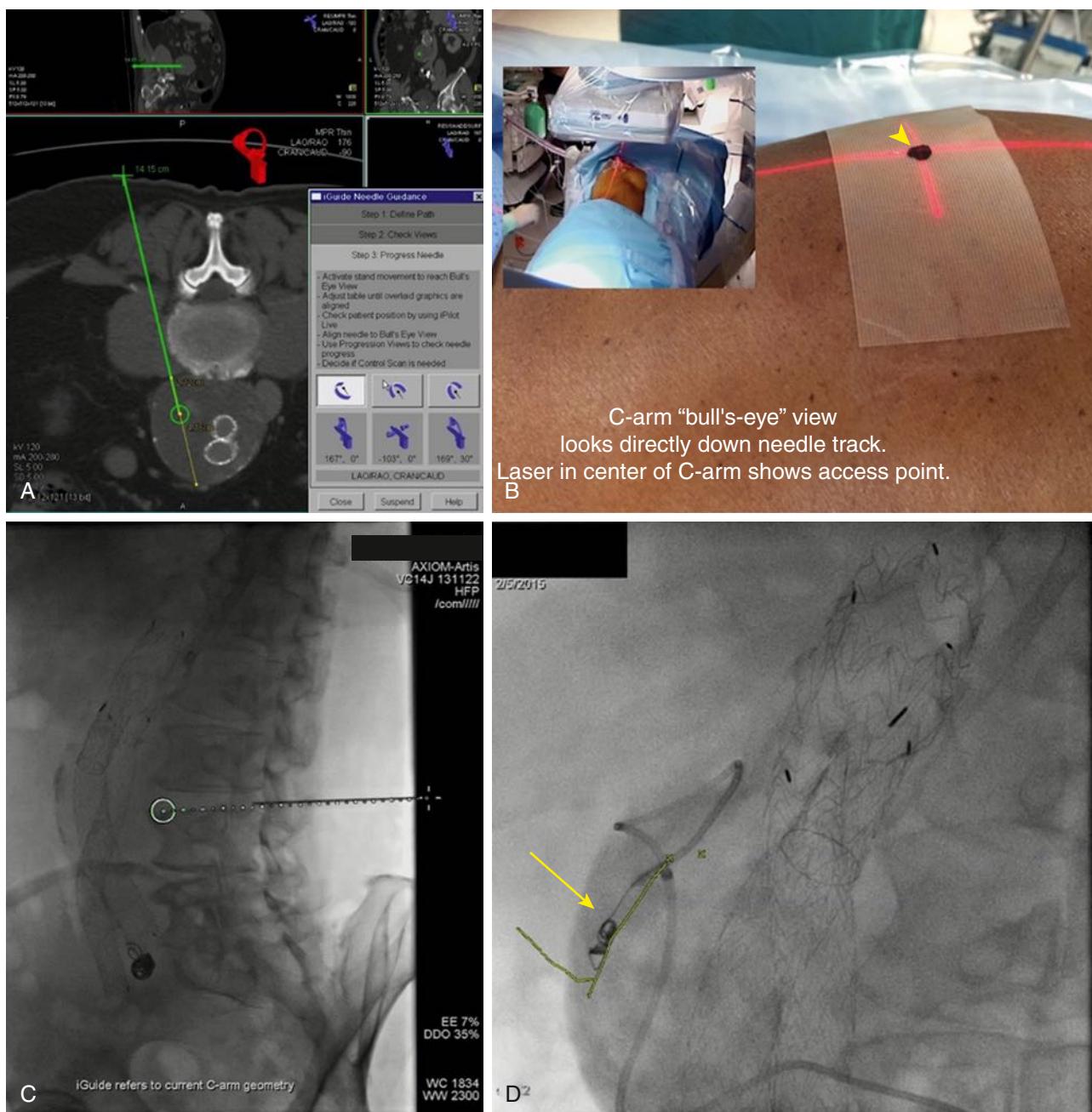
Once the target site is accessed by the needle, confirmation can be achieved with blood aspiration from endoleak site or by a repeat CBCT imaging. Then, a guide wire may be placed and a sheath positioned to continue with the embolization

procedure in standard fashion using embolization coils or liquid embolic agent.

### Challenges and Next Steps

One of the current challenges associated with image fusion is that most solutions do not typically consider the vascular deformation caused by stiff wires, devices placed inside the lumen of the blood vessels. There are two approaches currently being evaluated to limit this problem: (1) acquiring an intraoperative 3D dataset (CBCT) after the device-induced vessel deformation has occurred, and (2) deriving deformable registration of the pre-operative dataset by acquiring biplane fluoroscopic images of device and reconstructing the 3D device followed by development of algorithms that automatically compensate for iliac straightening and can predict the final position of the internal iliac artery origin. In addition, patient-related movements during the procedure need to be corrected automatically during image fusion.

A few more practical yet important challenges include optimization of preoperative CT or MR imaging protocols, and adequate training of the OR technologists and surgical team in using these advanced imaging and image fusion techniques. In addition, vascular pathologies such as aortic dissection, aortic endoleaks, and arteriovenous malformations are dynamic in nature. Hence, preoperative imaging and postoperative surveillance in these patients mandate an appropriate use of dynamic CT and MR imaging techniques. Furthermore, advance flow



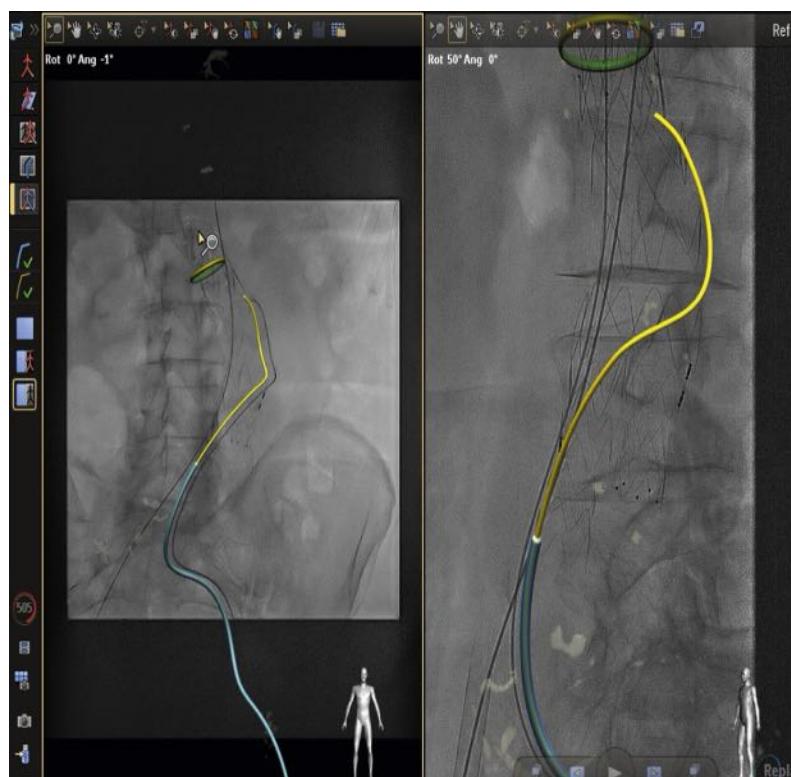
**Figure 33.8** (A) Virtual needle path. (B) “Bull’s-eye” view projected on the patient’s skin surface. (C) Lateral fluoroscopic live view of the needle path. (D) Image fusion with fiducial marker identifying the desired destination of coil embolization.

imaging techniques such as 4D-flow MRI have been evolving with faster image acquisition techniques such as compressed sensing and parallel imaging, which when combined with robust dynamic morphological imaging will enable objective quantification in guiding management of dynamic vascular pathologies such as aortic dissection.<sup>67,68</sup>

### Optical and Electromagnetic Tracking for Image Fusion and Guidance

Although image fusion is currently performed by fusing two DICOM datasets using 3D–3D fusion or using two fluoroscopic images using 2D–3D fusion, there are other methodologies for

fusing preoperative datasets in the OR. For example, nonradiation-based methods may be used: (1) electromagnetic tracking of sensors placed in the instruments and electromagnetic field generator placed in the surgical suite, or (2) optical scanning of the patient’s surface contours and fusing the surface to the surface rendered from the CT datasets. Such nonradiation-based fusion techniques could be much more cost-effective than using a conventional hybrid room and could potentially be used in every OR for surgical procedure guidance. For example, the incisions for minimally invasive cardiac surgical procedures could be optimized, such as localizing the left internal mammary artery to left anterior descending coronary artery bypass graft prior to surgical incision for a minimally invasive CABG procedure.



**Figure 33.9** FORS shape sensing technology allowing visualization of catheters/guide wires/etc. in full 3D shape.  
(Image courtesy Joost van Herwaarden.)

### Fiber Optic RealShape Technology

In vascular surgery practice, the mainstay of intraoperative imaging remains fluoroscopy, with no widespread efforts to replicate the concerted efforts to minimize the use of ionizing radiation as we have seen in other fields. Electrophysiologists have, for example, essentially abandoned fluoroscopy for electromagnetic (EM) tracking of catheters and devices. We have studied the feasibility of using this EM technology in aortic interventions coupled with robotics and found that ionizing radiation could be completely eliminated, thereby also decreasing contrast exposure and reducing operative time.<sup>69</sup> A recent advance in the field of procedural image guidance and device visualization led to the development of a promising new technology the Fiber Optic RealShape (FORS) technology (Philips Medical Solutions, the Netherlands), diminishing the operator's dependency on the use of fluoroscopy. The clinician is able to obtain 3D visualization of the full shape of devices inside the body, which facilitates performing endovascular procedures in a minimal-radiation setting.

FORS technology utilizes the application of light traveling through hair-thin optical fibers, and is based on the concept of measuring strain in the optical fibers using light reflected from density fluctuations in these fibers.

A 3D, real-time visualization of the shape of the devices can be achieved with distinctive colors and multiple viewing angles using the FORS technology. These devices can thus be shown in the context of the patient's specific anatomy through integration with preoperative CT or MR imaging guiding the operator in navigating through the patient's anatomy and

allowing precise positioning while visualizing catheters, guide wires and devices in full 3D shape (Fig. 33.9).<sup>70</sup>

## ENDOVASCULAR NAVIGATION AND CATHETER ROBOTICS

The Holy Grail of endovascular interventions would be to have impeccable control of not only the imaging but also the endovascular tools. The use of endovascular catheter robots represents yet another technological leap, which has the potential to transform endovascular navigation, providing a level of accuracy, maneuverability, and stability that cannot be achieved using manually controlled catheters. Since we are constantly working in a malleable 3D space, without coupling the catheter technology to real time imaging, the fluidity of endovascular procedures will always be marred.<sup>71-73</sup>

Currently there is only one catheter-based robotic system with FDA approval for peripheral interventions. That system is Corindus (Waltham, MA), although it is also the only flexible robotics platform without an actuated catheter and integrated imaging (Fig. 33.10 and Table 33.1).

Until recently, robotic catheters have not been integrated into the imaging system upon which all endovascular interventions are dependent. Developments will allow path planning from 3D reconstruction models, followed by semiautonomous movement of the catheter to a target, termed "assisted navigation." This, in our opinion, is the ultimate opportunity to integrate precise 3D navigation with high-resolution 3D imaging.<sup>74</sup> This novel "assisted" robotic navigation capability has

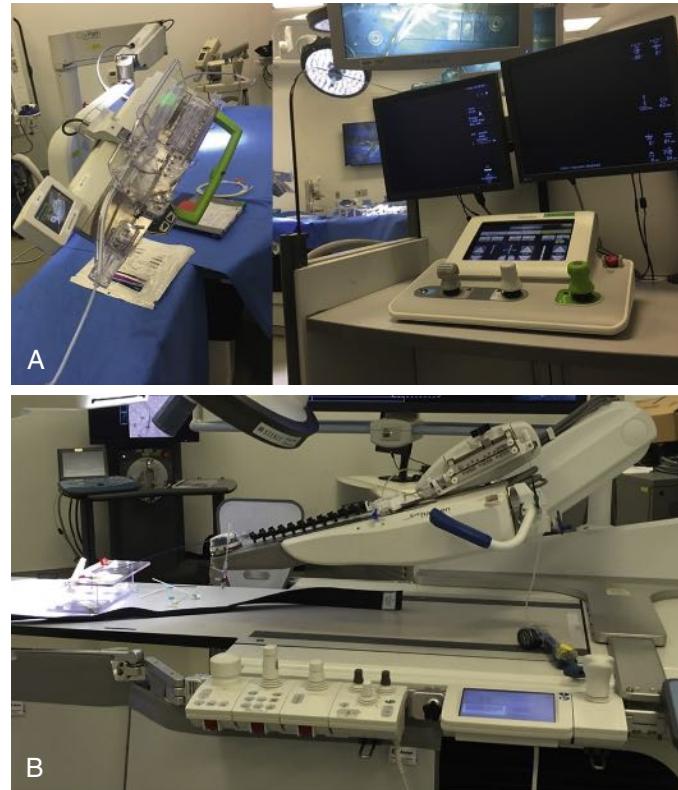
recently been demonstrated by Schwein et al. in an *ex vivo* aortic aneurysm model.<sup>74</sup> Continuous electromagnetic tracking provides feedback on catheter localization, shape, and motion using EM sensors embedded within the robotic catheter. Such electromagnetic triangulation of an EM enhanced robotic system permits feedback on catheter motion, correction of catheter movement, and autonomous movement along a predetermined trajectory. As noted above, future endovascular navigation will be enhanced by nonradiation-based

endovascular device localization, possibly facilitated by optical fiber-based or electromagnetic sensor-based tracking or other upcoming tracking technologies.

## THE FUTURE OF HYBRID OPERATING SUITES

The latest generation of hybrid operating rooms is evolving with integration of multiple imaging modalities for guiding minimally invasive therapies in vascular surgery. However, impact of “integrated multi-modality imaging” will be even greater if combined with novel catheter-based therapies and minimally invasive robotic surgical solutions. Making the process of multi-modality image integration with current generation and upcoming devices more user-friendly is a burden the vendors are obligated to solve using an open, intuitive vendor-neutral architecture platform. Certainly, in some of the existing systems there is significant variability in the ease of use. Additionally, it is imperative that the vendors make it a priority to ensure a consistent and effective process towards educating their users, by developing dedicated learning pathways for technologists, residents, fellows, and attending surgeons.

To bolster the intraoperative imaging capabilities, some future hybrid ORs are now increasingly being installed with integrated fully functional conventional multi-slice CT imaging systems. These CT imaging systems reside in the OR, mounted on the rails and slide over the patient whenever cross-sectional imaging is required. This could be a transformational technological development for minimally invasive image-guided surgery that can impact patient care directly. For example, unstable patients with suspected pulmonary embolism or aortic dissection may go straight to such a hybrid OR, where intensive care can be continued, a diagnosis can be confirmed or refuted, and therapy from lysis to open pulmonary thrombectomy, and aortic surgery can be immediately instituted. Such a room can transform trauma management, allowing immediate



**Figure 33.10** (A,B) Flexible robotics integration into the hybrid OR.

**TABLE 33.1** Catheter Based Robotics Systems. (Note: as of 2021 only Corindus has a vascular application)

Device	FDA Approved	Company	Integrated Imaging	Proprietary Flexible Catheter	Master/Slave	Automated Navigation
Magellan Robotic system*	Yes	Hansen Medical*	No	Yes	Yes	Yes experimental
CorPath GRX	Yes	Corindus	No	No	Yes	No
Monarch	Yes	Auris Health (acq. Johnson & Johnson)	Yes	Yes	Yes	No
Ion	Yes	Intuitive Surgical	Yes	Yes	Yes Fiberoptic shape sensing technology	No
superDimension Navigation System	Yes	Medtronic Inc.	Yes	Yes	Yes	No

\*No longer on the market

angiography, CT imaging, and appropriate therapy – either interventional or open surgical procedures instituted. However, these rooms also present some operational challenges in that cross-trained radiology technicians, knowledgeable in both angiography and CT scanning, and careful consideration of surgical workflows are necessary.

An additional imaging combination being explored is combined angiography suite and MRI imaging systems. An MRI must be kept in a magnetically isolated environment, separate from the main angiography suite or OR. Patients must be transported into the adjacent MRI imaging system using a dockable table transfer system whenever imaging is needed. Although having a dynamic imaging modality such as MRI is attractive, currently there are few uses for such a combination system in cardiovascular interventions; however, they are now being actively used in neurosurgery.

While the possibilities are endless, and “chance favors only the prepared mind,” it may be prudent to say that the future of minimally invasive endovascular and open surgery is bright at the very cusp of upcoming “novel imaging and navigation” technologies on the horizon.<sup>70</sup>

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# Preoperative Evaluation and Management

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Based on a previous edition chapter by G. Matthew Longo and Thomas G. Lynch

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## GENERAL PREOPERATIVE RISK ASSESSMENT

Every patient undergoing elective vascular surgery should have a preoperative assessment that includes a thorough history and physical examination focused on cardiovascular risk factors, blood analysis, and electrocardiogram (ECG). A complete blood count should be obtained to screen for the presence of infection, to ensure an adequate red blood cell volume, and to rule out a serious hematologic abnormality. Serum electrolyte concentrations should be evaluated and corrected when abnormalities exist. Of special importance are serum potassium, calcium, and magnesium levels because if they are abnormal and not corrected, they can lead to adverse cardiac events. Furthermore, because renal disease is so prevalent in vascular patients and some vascular interventions may compromise renal function, a baseline creatinine level and estimated glomerular filtration rate should be obtained. All patients should also have serum glucose concentration measured, and in diabetic patients a recent hemoglobin A<sub>1c</sub> concentration should be documented. Measures of coagulation, such as the partial thromboplastin time (aPTT), prothrombin time (PT), and

international normalized ratio (INR), should be determined to identify coagulation abnormalities; and in patients on anticoagulation, an appropriate strategy should be determined prior to surgery. Finally, overall assessment of health can be quantified by the American Society of Anesthesiologists (ASA) classification (Table 34.1).

### Cardiac Evaluation and Management

Despite optimal management of cardiovascular risk factors, major vascular surgery is associated with postoperative myocardial infarction in 1.6% of all patients, with higher risk after open abdominal aortic aneurysm repair or peripheral bypass. Postoperative myocardial infarction increases 1 year mortality from approximately 5% to 37%.<sup>1</sup> In addition to a thorough cardiac history, physical examination, and baseline ECG, advanced cardiac testing may be appropriate for selected patients undergoing elective vascular procedures. The American College of Cardiology (ACC) Foundation and the American Heart Association (AHA) have provided recommendations regarding preoperative cardiac workup (Fig. 34.1).<sup>2</sup> Perioperative risk stratification is based on a combination of patients' functional

**TABLE 34.1****American Society of Anesthesiologists' Classification**

<b>ASA I</b>	Normal, healthy patient with good exercise tolerance
<b>ASA II</b>	Controlled medical conditions without significant systemic effects
<b>ASA III</b>	Medical conditions with systemic effects; functional compromise
<b>ASA IV</b>	Medical condition with significant dysfunction; potential threat to life
<b>ASA V</b>	Critical medical condition; little chance of survival with or without surgery
<b>ASA VI</b>	Brain death, anesthesia performed for organ donation

ASA, American Society of Anesthesiologists.

status and the anticipated physiologic strain of surgery. Low risk vascular procedures with anticipated <1% 30-day major adverse coronary events (MACE) include carotid endarterectomy and carotid artery stenting in asymptomatic patients. Intermediate risk vascular procedures (1%–5% MACE within 30 days) include carotid endarterectomy and carotid artery stenting in symptomatic patients, peripheral artery angioplasty, and endovascular aneurysm repair. High risk vascular procedures (>5% MACE within 30 days) include open aortic surgery, limb revascularization or amputation, and thromboembolectomy.<sup>3,4</sup> Functional capacity is measured by metabolic equivalents (METS), where one MET is the basal metabolic rate of a 70-kg, 40-year-old man. Common activities requiring 4 METS include walking less than three flights of stairs, dancing, or light housework. Athletics (e.g. basketball, weight training) require ≥10 METS.<sup>5</sup> Asymptomatic patients with a functional capacity of 4–10 METS, those with a normal stress test within 2 years, and those who have had coronary revascularization within 5 years, do not need further cardiac testing. Stress testing may be indicated for patients at intermediate or high cardiac risk with poor or unknown functional capacity (<4 METs). Routine stress testing is not indicated for patients at low risk for noncardiac surgery.<sup>2</sup>

Patients with a pacemaker or an implantable cardioverter-defibrillator may require reprogramming or application of a magnet over the device to prevent the transient inhibition of pacing or the inappropriate triggering of shocks if monopolar electrocautery is used. Furthermore, external defibrillation equipment with transcutaneous pacing ability should be readily available in the operating room for these patients.

### Preoperative Medical Versus Interventional Therapy for Cardiac Disease

Perioperative use of beta blockers has long been the standard of care for most patients with cardiac disease undergoing vascular surgery. However, their use has engendered significant controversy during the past several years. The POISE (Peri-Operative ISchemic Evaluation) trial and the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography trial (DECREASE-IV) trials both showed some

benefit to beta blockade in selected groups of vascular patients, but both trials have had their results called into question.<sup>2,6,7</sup> In a review of nearly 12,000 patients undergoing infringuinal revascularization in the Vascular Quality Initiative (VQI) database, Shannon et al. showed that preoperative beta blockade was an independent predictor of 30-day MI and MACEs after controlling for other cardiovascular risk factors; there was no impact on short-term limb-related outcomes.<sup>8</sup> Another systematic review by Hajindebeh et al. examining more than 32,000 patients showed no change in outcomes when beta blockers were administered in the perioperative period.<sup>9</sup> In a separate systematic review, preoperative use of beta blockers was associated with a reduction of cardiac events, but support was lacking regarding the effectiveness of preoperative administration of beta blockers to reduce the risk of surgical death.<sup>10</sup> Furthermore, there is a clear association between beta-blocker administration and adverse outcomes, such as bradycardia and stroke. Likewise, withdrawal of chronic beta blockade has risk, including rebound tachycardia, and the use of these medications should be guided by individual circumstances for best medical therapy based on cardiovascular risk independent of the need for vascular surgery. Thus, the best recommendation for beta-blocker use is to continue them in patients who have been on them chronically. In patients with intermediate or high risk myocardial ischemia on preoperative risk stratification tests or with three or more Revised Cardiac Risk Index (RCRI) risk factors (e.g., diabetes mellitus, heart failure, coronary artery disease, renal insufficiency, stroke), it is reasonable to begin perioperative beta blockers in advance of surgery to assess safety and tolerability. Beta-blocker therapy should generally not be started on the day of surgery.<sup>2</sup>

Most other established medications should be continued throughout the perioperative period with the exception of angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs).<sup>2</sup> There is evidence that high intensity statins reduce the risk of adverse cardiovascular events, including mortality and limb loss, among high-risk patients and patients with peripheral arterial disease through their pleiotropic effects on endothelial function, reduction in vascular inflammation, and stabilization of atherosclerotic plaque.<sup>11,12</sup> In the absence of a specific contraindication or intolerance, statins should be initiated prior to surgery and be continued throughout the perioperative period (see Ch. 44, Systemic Complications: Cardiac).

Although many surgeons prefer to discontinue clopidogrel or other P2Y<sub>12</sub> inhibitors due to a perceived risk of increased bleeding at the time of surgery, there are scant objective data to support this practice. Several studies demonstrate the overall safety of continuing DAPT during vascular surgery,<sup>13,14</sup> though there may be a slightly higher risk of bleeding in exchange for a reduction in cardiovascular events.<sup>15,16</sup> Furthermore, the role of dual antiplatelet therapy (DAPT) in the management of coronary artery disease continues to evolve. Current ACC/AHA guidelines<sup>17</sup> support the use of DAPT following percutaneous coronary intervention (PCI) with both bare metal stents (BMSs) and drug-eluting stents

(DESs). The duration of DAPT is dependent on the indication (acute coronary syndrome vs. stable angina) and PCI technique (BMS vs. DES), balanced against the estimated risk of bleeding. If the risk of surgical bleeding is believed to be high, elective vascular procedures should be postponed until DAPT can be safely withheld. If the procedure is urgent DAPT should be continued, particularly during the first 4 to 6 weeks following stent implantation, unless the risk of bleeding outweighs the risk of coronary stent thrombosis. Consultation with cardiology is appropriate prior to discontinuing DAPT (see Ch. 42, Antiplatelet Agents).

The role of coronary revascularization prior to vascular surgery is uncertain. Generally, coronary revascularization is recommended for patients with left main coronary artery disease, three-vessel coronary disease, complex anatomy or high risk comorbidities.<sup>18</sup> The Coronary Artery Revascularization Prophylaxis (CARP) trial demonstrated that in patients with stable coronary artery disease, coronary artery revascularization before elective major vascular surgery does not improve long-term cardiac outcomes or reduce short-term postoperative outcomes such as death, MI, or length of hospital stay.<sup>19</sup> In addition, preoperative coronary artery revascularization in vascular patients is associated with increased risk for procedure-related complications and may lead to delay in the intended vascular procedure. Furthermore, patients with CABG or PCI <5 years prior to vascular surgery do not have a survival advantage over patients at high cardiac risk without previous coronary interventions. Therefore, ACC/AHA guidelines recommend preoperative revascularization only when it would otherwise be indicated in nonoperative situations.<sup>2</sup> Only patients with unprotected left main disease (the left main trunk is unprotected when there is a >50% stenosis and the absence of at least one patent bypass to the left circumflex or left anterior descending artery) showed a benefit from preoperative coronary artery revascularization. CABG showed improved outcomes versus PCI.<sup>20</sup>

## Preoperative Management of Hypertension

There is no consensus on specific perioperative blood pressure targets, although higher morbidity and mortality is associated with both hypotension and hypertension. For noncardiac surgery, the strongest recommendation is for an individualized approach to each patient maintaining a blood pressure within 90%–110% of baseline. For patients with a low baseline (SBP <90 mm Hg, DBP <50 mm Hg) it is recommended to maintain a MAP ≥60 mm Hg, and for patients with a high baseline (SBP ≥130, DBP ≥80), it is recommended to maintain the SBP <160 mm Hg.<sup>21</sup>

There is general consensus that chronic antihypertensive medications should be continued during the perioperative period, with the exception of ACEIs and ARBs. Withholding chronic ACEI/ARB therapy is associated with less intraoperative hypotension with no difference in all-cause death, stroke, and MI.<sup>21</sup> Intraoperative hypotension in patients who receive ACEIs or ARBs on the day of surgery has been associated

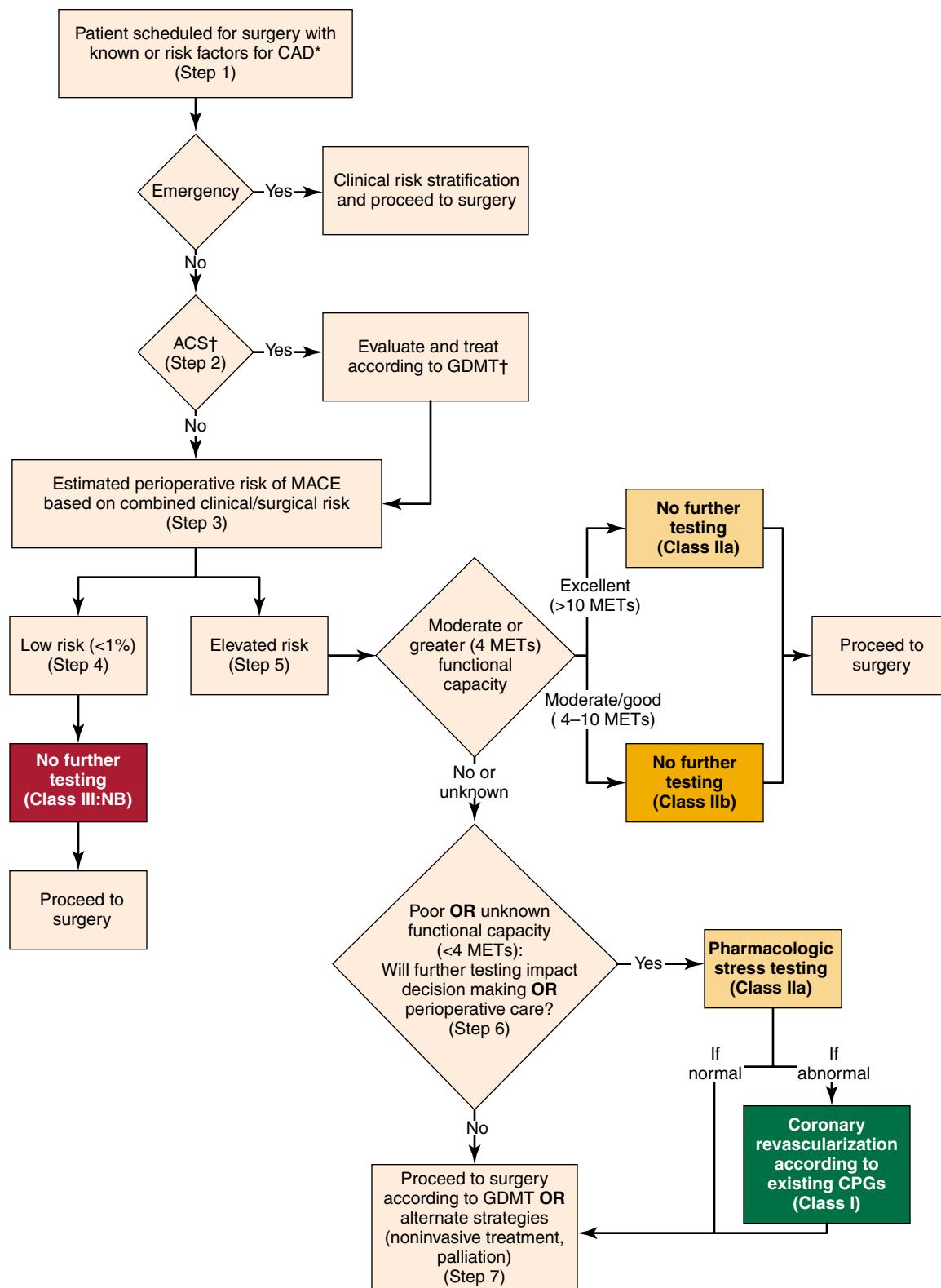
with an increased risk of all-cause death, stroke, and MI<sup>22</sup> (see Ch. 14, Hypertension).

## Pulmonary Evaluation and Management

Pulmonary complications are reported in 1% to 2% of minor surgeries and up to 20% in upper abdominal or thoracic operations.<sup>23</sup> As such, preoperative pulmonary evaluation should be completed in all patients and should begin with a history and physical examination, which is the most sensitive evaluation to identify patients at risk for complications. Risk factors for postoperative pulmonary complications include emergency procedure, age over 65 years, congestive heart failure, chronic obstructive pulmonary disease, functional status, tobacco use, operative time, ASA class ≥2, and procedure type (abdominal aortic aneurysm, thoracic, upper abdominal).<sup>24–27</sup> The surgeon should elicit any history of smoking, oxygen dependence, exercise intolerance, unexplained dyspnea, or coughing. On physical examination, decreased breath sounds, wheezes, crackles, or a prolonged expiratory phase should be noted. Procedure-related risks should likewise be assessed. Procedural time greater than 3 hours, need for emergent surgery, and the surgical site all influence the risk of perioperative pulmonary complications. Aortic aneurysm, thoracic, abdominal, and emergency surgery all increase the risk of pulmonary complications. Obstructive sleep apnea, which is present and often undiagnosed in up to 22% of the adult population undergoing surgical procedures, increases the chances of postoperative hypoxemia and reintubation in the postoperative period.<sup>28</sup>

Asymptomatic patients do not need routine preoperative chest X-rays, however a chest X-ray is recommended for patients with known cardiopulmonary disease, age >50 years, and if undergoing abdominal, thoracic, or abdominal aortic aneurysm surgery.<sup>23</sup>

Several indices can be used to stratify pulmonary risk. These include factors such as the type of surgery, age, functional status, weight loss/nutritional status, COPD, smoking, whether the surgery is emergent, and obstructive sleep apnea. Obstructive sleep apnea can be screened for using the validated snoring, tiredness, observed apnea, high blood pressure, neck circumference, male sex (STOP-Bang) score. Low serum albumin (<3.5 g/L) is a powerful, independent marker of increased risk for postoperative pulmonary complications. Pulmonary function testing should not be routinely obtained, but is useful in patients with underlying lung disease where clinical evaluation is either insufficient or unable to determine their baseline lung function to determine optimization strategies.<sup>29</sup> After a patient is identified as at risk for pulmonary complications, risk reduction strategies used include smoking cessation, respiratory physiotherapy, respiratory muscle training, and optimization of nutritional status. Intraoperative strategies include lung recruitment maneuvers, protective tidal volume of 6–9 mL/kg in non-injured lungs, positive end expiratory pressure of 10 cm H<sub>2</sub>O to reduce atelectasis, and postoperative lung expansion techniques<sup>30</sup> (see Ch. 45, Systemic Complications: Respiratory).



**Figure 34.1 Stepwise Approach to Perioperative Cardiac Assessment for CAD.** Colors correspond to the Classes of Recommendations in Table 34.1. **Step 1:** In patients scheduled for surgery with risk factors for or known CAD, determine the urgency of surgery. If an emergency, then determine the clinical risk factors that may influence perioperative management and proceed to surgery with appropriate monitoring and management strategies based on the clinical assessment. **Step 2:** If the surgery is urgent or elective, determine if the patient has an ACS. If yes, then refer patient for cardiology evaluation and management according to GDMT according to the UA/NSTEMI and STEMI CPGs. **Step 3:** If the patient has risk factors for stable CAD, then estimate the perioperative risk of MACE on the basis of the combined clinical/surgical risk. This estimate can use the American College of Surgeons NSQIP risk calculator (<http://www.surgicalriskcalculator.com>) or incorporate the RCRI with an estimation of surgical risk. For example, a patient undergoing very low-risk surgery (e.g., ophthalmologic surgery), even with multiple risk factors, would have a low risk of MACE, whereas a patient undergoing major vascular surgery with few risk factors would have an elevated risk of MACE. **Step 4:** If the patient has a low risk of MACE (<1%), then no further testing is needed, and the patient may proceed to surgery. **Step 5:** If the patient is at elevated risk of MACE, then determine functional capacity with an objective measure or scale such as the DASI. If the patient has moderate, good, or excellent functional capacity ( $\geq 4$  METs), then proceed to surgery without further evaluation. **Step 6:** If the patient has poor (<4 METs) or unknown functional capacity, then the clinician should consult with the patient and perioperative team to determine whether further testing will impact patient decision making (e.g., decision to perform original surgery or willingness to undergo CABG or PCI, depending on the results of the test) or perioperative care. If yes, then pharmacologic stress testing is appropriate. In those patients with unknown functional capacity, exercise stress testing may be reasonable to perform. If the stress test is abnormal, consider coronary angiography and revascularization depending on the extent of the abnormal test. The patient can then proceed to surgery with GDMT or consider alternative strategies, such as noninvasive treatment of the indication for surgery (e.g., radiation therapy for cancer) or palliation. If the test is normal, proceed to surgery according to GDMT. **Step 7:** If testing will not impact decision-making or care, then proceed to surgery according to GDMT or consider alternative strategies, such as noninvasive treatment of the indication for surgery (e.g., radiation therapy for cancer) or palliation. ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; CPG, clinical practice guideline; DASI, Duke Activity Status Index; GDMT, guideline-directed medical therapy; HF, heart failure; MACE, major adverse cardiac event; MET, metabolic equivalent; NB, no benefit; NSQIP, National Surgical Quality Improvement Program; PCI, percutaneous coronary intervention; RCRI, Revised Cardiac Risk Index; STEMI, ST-elevation myocardial infarction; UA/NSTEMI, unstable angina/non-ST-elevation myocardial infarction; VHD, valvular heart disease. (Reprinted with permission from Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;64:e77–e137.)

\*Please see full text of AHA clinical practice guidelines for recommendations for patients with heart failure, valvular heart disease, or arrhythmias.

†Please see full text of AHA clinical practice guidelines for UA/NSTEMI, and STEMI.

Patients who currently smoke have a twofold increased risk for postoperative complications, with the highest risk in patients who have smoked within the past 2 months. Smoking abstinence can reduce the rate of such complications. Patients who have quit smoking for more than 6 months have a risk similar to those who do not smoke, and the beneficial effects of smoking cessation, including improvement in ciliary function and a decrease in sputum production, occur gradually over a period of several weeks. Physician counseling alone can aid in smoking cessation.<sup>31</sup> Pharmacologic strategies to improve the quit rate for smoking include nicotine replacement therapy, bupropion, hypnosis therapy, and varenicline. Nicotine replacement therapy is available in several formulations, including transdermal patch, gum, nasal spray, inhaler, and lozenge. Bupropion is an atypical antidepressant, and varenicline is a partial agonist of the  $\alpha 4\beta 2$  nicotinic acetylcholine receptor. Second line agents are nortriptyline and clonidine which are not approved by the FDA for this purpose but can be effective as smoking cessation adjuncts. Brief counseling by physicians can aid in smoking cessation. A focused protocol to offer advice on smoking cessation, referral to telephone-based program (1-800-QUITNOW), and initial nicotine replacement and pharmacologic assistance has been developed by the Vascular Physicians Offer and Report (VAPOR) investigators.<sup>32</sup>

For patients with a history of bronchospasm and chronic obstructive pulmonary disease, guidelines suggest the use of inhaled bronchodilators,  $\beta 2$  agonists, and anticholinergics as the mainstays of symptomatic therapy for patients with bronchial hyperreactivity. These interventions should begin at least 5 days before surgery. Systemic or inhaled corticosteroids have been recommended when the FEV1 is less than 80% of predicted in anticipation of general anesthesia.<sup>33</sup> Chronic steroid dosing can be increased or decreased, and can be given intraoperatively depending on the underlying COPD severity and duration

of surgery.<sup>34–36</sup> In addition, instances of bronchospasm during intubation in patients with bronchial hyperreactivity not previously receiving bronchodilators are reduced with the use of albuterol and oral or inhaled steroids.<sup>33</sup> The safety of perioperative corticosteroid use has been established, and it is not associated with death or serious infections. Lung expansion techniques, such as incentive spirometry, chest physical therapy, cough, postural drainage, ambulation, and continuous positive airway pressure, have been used to limit postoperative pulmonary complications, although no single modality is clearly superior, and there is little benefit to combining modalities.<sup>29</sup> Despite the association of hypoalbuminemia with postoperative pulmonary complications, preoperative nutritional supplementation has not been shown to reduce incidence, however control of intra- and postoperative fluid resuscitation can.<sup>37–39</sup>

## Renal Evaluation and Management

Vascular patients are frequently found to have renal dysfunction. One-third of all vascular surgery patients suffer from stage III or higher chronic kidney disease (CKD).<sup>40,41</sup> Therefore kidney function must be carefully evaluated preoperatively, and this evaluation should include an assessment for the presence of renal failure symptoms, signs of hyperkalemia, volume status, anemia, and bleeding. In all patients a baseline creatinine level and glomerular filtration rate (GFR) should be obtained. If the patient is being maintained with dialysis, examination of the vascular access site should be inspected for signs of infection and functionality.

It is important to optimize potassium levels prior to intervention because hyperkalemia may cause cardiac instability. Treatment options include polystyrene binding resins, insulin and intravenous dextrose, calcium carbonate for cardiac stabilization, intravenous bicarbonate, and dialysis. Polystyrene

binding resins such as kayexalate can be given orally to remove excess stores of potassium. Patients maintained with dialysis should undergo dialysis the day before surgery in nonemergent situations. In addition to correction of electrolytes, acid–base balance should be achieved before surgery.

In the patient with renal dysfunction, uremia-associated platelet dysfunction may result in an increased incidence of perioperative bleeding. If confirmed, options to improve platelet function include dialysis, desmopressin (DDAVP), cryoprecipitate, and transfusion of red blood cells or platelets. Antiplatelet agents should be held prior to surgery, if feasible. In addition, drug-induced minor platelet effects may be exaggerated in ESRD patients, and drugs associated with such problems include diphenhydramine, nonsteroidal anti-inflammatory drugs, chlordiazepoxide, and cimetidine. Finally, decreased intraoperative heparin dosing should be considered in ESRD patients.

Anemia is often present in patients with ESRD due to decreased production of erythropoietin. If necessary, red blood cells can be transfused before emergency surgery, however unnecessary transfusion should be avoided because antibody formation may result in higher perioperative complications as well as increased rejection risk in future renal transplantation. In addition, transfusion may result in red blood cell lysis and contribute to hyperkalemia. If surgery is elective, it should be delayed until erythropoietin can be administered and the hematocrit allowed to increase in response.<sup>42</sup> Intravenous iron, vitamin B12, and oral folate can also be considered for treatment of anemia prior to elective surgery where high volume blood loss is expected.<sup>43</sup>

Contrast-induced nephropathy (CIN) is a significant problem as more patients are receiving iodinated contrast media.<sup>44</sup> Strategies to reduce the risk of CIN include: (1) avoidance of iodinated contrast by using alternative imaging techniques (e.g., MRA, ultrasound); (2) limiting the volume of iodinated contrast agents; (3) using only nonionic, low osmolar agents (e.g., iodixanol [Visipaque]); (4) complete avoidance of iodinated contrast by using CO<sub>2</sub>; and (5) judicious periprocedural hydration with isotonic saline. There is conflicting and insufficient data to recommend the use of N-acetylcysteine, IV sodium bicarbonate, ascorbic acid, statins, low-dose dopamine, or fenoldopam to reduce the incidence of CIN.<sup>45,46</sup> The use of a gadolinium-based agent, such as those used in magnetic resonance imaging, should be avoided in the setting of compromised renal function. Gadolinium has been associated with the development of nephrogenic systemic sclerosis, a rare but serious and sometimes fatal syndrome that involves fibrosis of the skin, joints, eyes, and internal organs (see Ch. 46, Systemic Complications: Renal).

## Diabetes Evaluation and Management

Preoperatively, the surgeon should elicit a complete diabetic history, including a history of metabolic control and complications including previous episodes of diabetic ketoacidosis or hyperosmolar hyperglycemic nonketotic coma. In addition, evidence of diabetic autonomic neuropathy should be sought

as this predisposes patients to perioperative hypotension, and gastroparesis increases a patient's risk for aspiration.

High glucose levels are associated with increased morbidity and mortality after surgery. Independent of cardiac disease, diabetes, or other comorbid conditions, hyperglycemia at the time of carotid endarterectomy has been associated with an increased risk for perioperative stroke, MI, and death.<sup>47</sup> In addition, poor perioperative glycemic control is associated with increased risk of death, major amputation, and graft occlusion after peripheral bypass surgery.<sup>48</sup> Therefore, it is imperative that blood glucose be controlled during and after surgery. When possible, glucose control should be attained weeks before surgery; hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) is a useful diagnostic test for assessing long-term glucose control. Some patients will require preoperative hospitalization and endocrine consultation to ensure diabetic control before surgery.

Several studies add additional perspective to perioperative glucose management in vascular surgery. Long et al. reviewed 1051 patients undergoing vascular procedures and found that 34.8% of patients had perioperative hyperglycemia. Multivariate logistic regression analysis showed a strong association between hyperglycemia and 30-day mortality as well as myocardial infarction, stroke, renal failure and wound complications.<sup>49</sup> Additionally, Vogel et al. reviewed the Cerner database in 3586 patients undergoing elective lower extremity revascularization and found that 22% of patients had hyperglycemia during their hospitalization, which was associated with higher acute complications, infection rates, and longer hospital stays.<sup>50</sup> Most recently, McGingle et al. reported an increased rate of limb loss, major adverse cardiac events, and an 8% increase in major adverse limb events for every category increase in patients with HbA<sub>1c</sub> <7%, 7%–10%, and >10% for patients undergoing lower extremity bypass.<sup>51</sup> In addition, Hirashima et al. demonstrated that strict postoperative glucose control significantly reduced the risk of wound infection in patients undergoing lower extremity bypass surgery.<sup>52</sup> Glucose control should also be considered in the nondiabetic patient, though data specifically examining patients undergoing vascular surgery are scant. Nair et al. retrospectively reviewed over 2000 patients undergoing noncardiac surgery and demonstrated that even in nondiabetic patients, higher mean glucose and high glycemic variability were associated with longer length of stay and greater risks of complications.<sup>53</sup> O'Sullivan and associates also found a link between poor preoperative glucose control in nondiabetics and perioperative mortality.<sup>54</sup>

While available data point to hyperglycemia being a risk factor for multiple complications, large-scale prospective data about active treatment of hyperglycemia leading to improved perioperative outcomes are lacking. Over the last several years trials have failed to support the concept of intensive blood glucose control improving perioperative outcomes. The use of intensive insulin therapy has been demonstrated to have no effect on mortality, sepsis, or wound infection.<sup>55</sup> Similarly, the need for strict intraoperative glycemic control has not been demonstrated. There continues to be insufficient evidence to provide definitive recommendations for glycemic targets for hospitalized patients. The Centers for Disease Control and

Prevention,<sup>56</sup> American Diabetes Association,<sup>57</sup> and others have recommendations on inpatient glycemic control.<sup>58</sup> Current recommendations are that a target glucose level of <200 mg/dL should be maintained in both diabetic and non-diabetic patients after surgery; data are lacking to recommend more intensive glucose postoperatively, or specific HbA<sub>1c</sub> targets preoperatively.<sup>56</sup>

Different regimens have been recommended for routine preoperative treatment of diabetic patients undergoing surgical procedures. Oral agents are generally withheld the day of surgery, and hyperglycemia can be corrected with insulin. Metformin should be stopped 24 hours before surgery to prevent the rare but possible adverse effect of lactic acidosis if the patient's renal function becomes compromised. Specific sliding scale insulin regimens are utilized on the basis of hospital-based guidelines (see Ch. 12, Diabetes).

## Adrenal Evaluation and Management

Patients who have been chronically treated with steroids are at risk for a postoperative adrenal crisis. A careful history should screen for steroid use or other causes of primary or secondary adrenal insufficiency. Hypothalamic or pituitary dysfunction should be considered in patients with tumors, previous brain irradiation, or sarcoidosis. Furthermore, primary adrenal insufficiency may be present in patients with tuberculosis, acquired immunodeficiency syndrome, and autoimmune endocrine syndromes. Patients taking ≥5 mg of prednisone per day (or equivalent), less than 5 mg of prednisone (or equivalent) but in the evening, or patients who have discontinued glucocorticoids in the year prior to surgery can be evaluated for adrenal insufficiency by measuring a morning cortisol level or assessing the results of a corticotropin stimulation test to identify adrenal insufficiency.<sup>59</sup>

Marik and Varon performed a literature review to determine the requirement for perioperative stress doses of corticosteroids in patients receiving long-term corticosteroid therapy and concluded that patients receiving therapeutic doses of corticosteroids do not require supplemental coverage if daily doses are continued.<sup>60</sup> However, the Association of Anaesthetists, the Royal College of Physicians, and the Society for Endocrinology UK have published guidelines for glucocorticoid management during the perioperative period in patients with adrenal insufficiency. They recommend that patients receiving daily corticosteroids (5 mg or more of prednisone, or equivalent) should receive supplemental stress dose steroids perioperatively. Hydrocortisone 100 mg IV should be administered at the time of anesthesia induction followed by continuous infusion of 200 mg/day until transition to double oral glucocorticoid dosing can be resumed. This regimen should be maintained for 48 hours post-procedure, and in some patients up to one week, depending on case complexity and individual response.<sup>61</sup>

Patients taking less than 5 mg of prednisone (or equivalent) in the morning, treated for less than 3 weeks, or taking less than 10 mg of prednisone (or its equivalent) every other day should not require intraoperative steroid coverage in addition to their daily dose. Although perioperative steroid use may be

associated with impaired wound healing, increased blood glucose concentration, or increased susceptibility to infection, a recent meta-analysis showed that a single dose of perioperative dexamethasone resulted in no difference in the risk of perioperative wound or systemic infection.<sup>62</sup>

## Coagulation Evaluation and Management

### Preoperative Anemia and Coagulation Assessment

Preoperative anemia increases the postoperative morbidity and mortality for patients undergoing noncardiac surgery. A history of chronic renal disease or anemia as well as a preoperative hematocrit level should be obtained prior to surgery. Ideally, preoperative anemia should be identified and treated if possible. Bleeding from the gastrointestinal or genital–urinary tract should be considered and investigated. There are three types of iron-restricted erythropoiesis that should be considered: absolute iron deficiency, iron sequestration secondary to inflammation, and iron deficiency due to insufficient erythropoiesis stimulating agents.<sup>63</sup> Nutritional deficiencies also need consideration. These forms of anemia can be treated with pharmacologic interventions, including iron, vitamin and folate supplementation, or erythropoiesis-stimulating agents. Transfusion of blood preoperatively should be limited to patients who are symptomatic, bleeding with severe anemia, or poor physiologic reserve with insufficient time to correct the physiologic abnormality. However, because transfusion is not without side effects and cost, anemic patients should be carefully evaluated to determine whether transfusion is necessary. The patient's cardiac status may influence the decision to transfuse, as anemia worsens outcomes in patients with coronary artery disease who undergo cardiac or noncardiac surgery. Most current guidelines recommend adhering to a restrictive transfusion strategy when possible.<sup>64</sup> In adult patients, transfusion should be considered at hemoglobin concentrations of 7 g/dL or less. In patients with symptomatic coronary disease, transfusion should be considered at a hemoglobin concentration of 8 g/dL or less.<sup>65,66</sup> For elective surgery, preoperative administration of erythropoietin, intravenous iron, vitamin B<sub>12</sub>, and folic acid should be considered to boost the patient's red blood cell volume from endogenous sources.<sup>43</sup> Autologous transfusion of previously banked blood, or use of intraoperative autotransfusion can also be considered.

Due to the nature of most vascular surgical interventions, and the fact that most vascular patients are on antiplatelet agents or anticoagulants, coagulation studies are routinely checked. However, the medical history remains the most important tool for detecting inherited and acquired bleeding disorders that would increase the risk of perioperative bleeding. This includes a medication history, questions regarding a known coagulopathy, unexplained epistaxis, hematomas, prolonged bleeding following cuts or abrasions, or abnormal requirements for blood products after previous surgeries. Routine tests include an activated partial thromboplastin time (aPTT), a PT, which allows the generation of the standard INR, and a platelet concentration. Unfortunately, these values are poor predictors of perioperative bleeding and mortality, although an INR greater than 1.8 and a platelet count less than  $50 \times 10^3$  have been associated

with adverse outcomes and may delay surgery or prompt an intervention to correct the abnormality<sup>67</sup> (see Ch. 39, Disorders of Coagulation: Hemorrhage).

### Venous Thromboembolism Prophylaxis, Thrombotic Risk Factors, and Antithrombotic Therapy

The potential for VTE and its complications in surgical patients can be stratified by risk factors and the type of operation. Prior to surgery, the surgeon should obtain a history of the patient's coagulation status and previous history of thrombotic events. A family history or a previous episode of deep vein thrombosis (DVT) may indicate a genetic predisposition to clotting abnormalities. A pharmacologic history, including current and previous exposure to drugs that modify coagulation and platelet function, as well as possible adverse reactions, such as aspirin allergy or history of heparin-induced thrombocytopenia (HIT), should also be obtained. In addition, physicians should inquire about procoagulant states, such as prothrombin gene mutation, factor V Leiden mutation, antithrombin III deficiency, protein C and S deficiency, antiphospholipid antibody (APLA) syndrome, disseminated intravascular coagulation, and abnormal platelet function, all of which may confound the underlying disease process responsible for the vascular insult (see Ch. 40, Disorders of Coagulation: Hypercoagulable States).

Pharmacologic prophylaxis for VTE includes unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), fondaparinux, warfarin, antiplatelet therapy, and direct oral anticoagulants (DOACs). Mechanical devices, such as graduated

compression stockings, intermittent pneumatic compression, and venous foot pumps, are also effective modalities for prophylaxis of venous thromboembolism (see Ch. 147, Venous Thromboembolic Disease: Mechanical and Pharmacologic Prophylaxis). Clinical practice guidelines for VTE prophylaxis have been reported.<sup>68</sup> Recommendations specific to vascular surgery are limited due to the lack of large randomized trials evaluating outcomes in patients undergoing specific vascular procedures. It has been shown that vascular and cardiac surgery patients have a higher risk of VTE compared to general surgery patients in the NSQIP database.<sup>69</sup> Recommendations for vascular surgery have been pooled with recommendations for patients undergoing other noncardiac surgeries (Table 34.2).

Perioperative management of anticoagulation should focus on both the need to discontinue any chronic anticoagulation and the necessity to initiate bridge anticoagulation prior to and after surgery. Consensus recommendations have been published by the American College of Surgeons regarding the timing of cessation of anticoagulation prior to scheduled surgery. These include holding warfarin for 5 days, dabigatran for 2–4 days depending on renal function, DOACs for 2 days for high-bleeding risk procedures and 1 day for low-bleeding risk procedures, and antiplatelet agents for 5–7 days (for operations not requiring DAPT).<sup>70</sup>

Consensus recommendations support the use of bridging anticoagulation with either therapeutic LMWH or intravenous unfractionated heparin in high-risk patients.<sup>71</sup> High-risk patients include those with atrial fibrillation and a high risk of embolic stroke or systemic embolic event within the

**TABLE 34.2** Reversal Agents for Anticoagulants

Anticoagulant	Anticoagulant Route of Administration	Mechanism	Reversal Agent	Reversal Agent Dosing	Reversal Agent Route of Administration
Dabigatran (Pradaxa)	Oral	Direct thrombin inhibitor	Idarucizumab (Praxbind) Activated PCC (FEIBA) if idarucizumab not available Hemodialysis	5 g 50–80 units/kg	IV IV
Apixaban (Eliquis) Rivaroxaban (Xarelto)	Oral	Oral factor Xa inhibitor	Andexanet alfa (AndexXa) Or 4 factor PCC	800 mg bolus followed by 960 mg infusion ( $\frac{1}{2}$ dose bolus/infusion if subtherapeutic)* 2000 units, or 25–50 units/kg	IV
Warfarin sodium (coumadin)	Oral	Vitamin K antagonist	Vitamin K PCC FFP	10 mg 5–10 mg 2000 units, or 25–50 units/kg 12–15 mL/kg	IV Oral IV IV
Unfractionated heparin	Intravenous	Antithrombin activation, factor Xa inactivation	Protamine Sulfate	1 mg/100 units of heparin	IV (max 100 mg/2 h for adults, 50 mg/2 h for children and adolescents)
Low-molecular-weight heparin	Subcutaneous	Antithrombin activation, factor Xa inactivation	Protamine Sulfate	0.5–1 mg/mg UFH	IV

\*If given <8 h since last dose of Apixaban or Rivaroxaban; half-dose Andexanet alfa if last DOAC dose >8 h prior.

FEIBA, factor eight inhibitory bypassing activity; FFP, fresh frozen plasma; IV, intravenous; PCC, prothrombin complex concentrate.<sup>96–98</sup>

past 3 months, any mechanical aortic valve with additional stroke risk factors, any mechanical mitral valve prosthesis, recent coronary stenting within the past 12 weeks, or prior thromboembolism during interruption of chronic anticoagulation.<sup>72</sup> Patients with atrial fibrillation are at high risk if they have a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 2 or greater in men or 3 or greater in women, have had a recent (within 3 months) stroke or TIA, or have a history of rheumatic valvular heart disease. Patients with a recent (within 3 months) history of venous thromboembolic disease or thrombophilia are also at high risk. Whether to bridge a patient for surgery, as well as the decision to resume anticoagulation after surgery, depends on the risk of bleeding in the judgment of the surgeon; but generally, resumption of anticoagulation should occur 12–24 hours after surgery. It is important to know which reversal agents are available for anticoagulants, including DOACs, which vary by institution<sup>70</sup> (Table 34.2). When managing anticoagulation bridging prior to the use of spinal or epidural anesthesia, prophylactic LMWH should be discontinued 10 to 12 hours prior to placement of the catheter and should be resumed 6 to 8 hours after catheter removal. When using therapeutic doses of LMWH, treatment should be discontinued 24 hours prior to catheter placement and restarted 24 hours after catheter removal.

The use of bridging anticoagulation in patients not at high risk is unclear, and individual risk factors for thromboembolic complications and perioperative bleeding need to be considered. Data regarding bridging for patients taking vitamin K antagonists (VKAs) specific to vascular surgery are lacking. However, data regarding percutaneous coronary intervention would indicate that uninterrupted therapy with VKAs is safer than bridging. A meta-analysis of eight studies reviewed comparisons of uninterrupted VKAs, VKA cessation without bridging, and VKA cessation with bridging. Patients that continued VKA treatment uninterrupted prior to PCI had a 65% lower risk of bleeding compared to patients that had interrupted treatment with bridging, with no change in the risk of major adverse cardiovascular and thrombotic events. Patients treated with continuous therapy had no difference in outcomes compared to patients that held anticoagulation without bridging.<sup>73</sup> This would indicate that patients being treated with VKA undergoing percutaneous vascular procedures may be better treated by forgoing bridging, and that high-risk patients for thrombotic events may be better treated by uninterrupted oral anticoagulation. In addition, a separate randomized, double-blind placebo-controlled trial in which patients with atrial fibrillation were assigned to receive LMWH bridging (100 IU/kg of dalteparin subcutaneously BID) or placebo after interruption of warfarin therapy revealed that forgoing bridging anticoagulation was noninferior to perioperative LMWH bridging with respect to the prevention of arterial thromboembolism and a decreased risk of bleeding.<sup>74</sup>

With the advent of DOACs such as dabigatran, rivaroxaban, apixaban, and edoxaban, there are additional considerations. The newer agents are frequently not monitored, have dependable therapeutic profiles, and have rapid onset and short half-lives, altering the time needed to clear the anticoagulant effect

and achieve clinical anticoagulation. A 2018 review of DOAC use in vascular surgery found limited data specific to the vascular patient population and in general, there are no recommendations for bridging in patients being treated with DOACs. DOACs should be stopped 2 days prior to a procedure with high bleeding risk, 1 day for low risk, and should be resumed 48–72 hours after a high risk, and 24 hours after a low risk procedure.<sup>75</sup> Small series have shown the feasibility of a DOAC bridge to and from a vitamin K antagonist for chronic anticoagulation as an alternative to LMWH and this is used in clinical practice; however this has not been studied in large trials. For patients receiving neuraxial anesthesia, the American Society of Regional Anesthesia recommends stopping prophylactic dabigatran 34 hours prior to surgery (two half-lives), and therapeutic doses up to 5 days prior to surgery.<sup>76</sup> Postoperatively, anticoagulants can be resumed at preoperative dosages once hemostasis has been ensured.

The American Society of Hematology acknowledged that cardiac and vascular surgical patients routinely receive high doses of intraoperative intravenous unfractionated heparin. In the 2019 guidelines for management of VTE in hospitalized surgical patients they suggest consideration of VTE chemoprophylaxis with unfractionated heparin vs. LMWH in addition to mechanical VTE prophylaxis with intermittent pneumatic compression or graduated compression stockings.<sup>77</sup> In 2018 the National Institute for Health and Care Excellence (NICE) guidelines provided specific recommendations for undergoing vascular surgery. For aneurysm repair and amputation, a minimum of 7 days of pharmacological prophylaxis with LMWH was recommended in addition to mechanical prophylaxis, continued until a significant reduction in mobility was no longer present after amputation. VTE prophylaxis was not recommended for varicose vein surgery if total anesthesia time is less than 90 minutes in low-risk patients. For anesthesia time over 90 minutes or if VTE risk outweighs bleeding risk, pharmacological and mechanical VTE prophylaxis was recommended.<sup>78</sup>

## Infection Evaluation and Management

Active infection in the preoperative period should be identified and considered when risk stratifying patients because of the risk for surgical site infection and perioperative decompensation. Common sources of pre- and postoperative infection include the urinary tract, the pulmonary system, an ischemic extremity, and previously placed prosthetic material. A history should be performed to elicit signs of infection such as recent fever, productive cough, urinary symptoms, tenderness or erythema over a graft, or drainage from an open wound or ischemic extremity. The physical examination should include evaluation of breath sounds and careful inspection to identify any ulceration, tenderness, or erythema. Urinalysis, a chest radiograph, and a white blood cell count should be obtained if indicated. If infection is identified, surgery should be delayed if possible. Choice of antibiotics should be tailored to the specific microbe and sensitivities identified from cultures. In the absence of an acute infection, perioperative prophylactic antibiotic administration is recommended in patients undergoing vascular surgery.

Preoperatively, patients should shower or bathe with soap or an antiseptic agent the night before surgery.<sup>79</sup> Normothermia, adequate volume replacement, and glycemic control (glucose <200 mg/dL) should be implemented in the perioperative period. Alcohol-based antiseptic agent should be used for skin prep unless contraindicated. Antibiotics should be administered within 1 hour before incision and should be discontinued once the skin incision is closed for clean and clean-contaminated cases, even if a drain is left in place.<sup>56</sup> Acceptable prophylactic antibiotics include cefazolin and cefuroxime. Clindamycin and vancomycin are acceptable alternatives in the setting of a  $\beta$ -lactam allergy, and vancomycin can be used in the setting of methicillin-resistant *Staphylococcus aureus* (MRSA) colonization or infection, chronic wound care, dialysis, acute inpatient hospital or nursing home care in the previous 12 months, or preoperative length of stay of >24 hours. Antibiotic choice should be tailored per institution-specific practice patterns, antibiograms, and infectious disease recommendations.

Antibiotic resistance is a growing problem, particularly with MRSA, which has become a predominant cause of *S. aureus* infections in both healthcare and community settings. Unlike for traditional *S. aureus* infection, treatment options for MRSA infection are limited and less effective. MRSA is typically transmitted person to person, and colonization generally precedes infection. Colonization is frequently long lasting (months to years). Successful prevention of MRSA transmission is possible through Centers for Disease Control and Prevention–recommended core and supplemental strategies. Core preventive strategies include assessing hand-hygiene practices, implementing contact precautions of MRSA-colonized/infected patients, recognizing previously colonized patients who have not met criteria allowing discontinuation of isolation, rapid laboratory reporting of MRSA identification, and providing MRSA education to healthcare providers. Studies of neurosurgical procedures and orthopedic procedures have shown reduction in surgical site infection with pre-procedure screening and de-colonization.<sup>80,81</sup> This has been met with controversy and has not been widely adopted in vascular surgery.

## Nutrition Evaluation and Management

Up to half of surgical patients have preoperative malnutrition that contributes to an increased risk for postoperative complications, such as impaired wound healing and infection, pulmonary complications, longer hospital stay, higher health cost, and overall increased morbidity and mortality. Vascular surgical patients are often elderly with poor mobility and diet, and multiple comorbidities that contribute to a higher prevalence of malnutrition. Malnutrition is also commonly exacerbated by specific chronic cardiovascular risk factors and disease processes such as diabetes, renal failure, and chronic mesenteric ischemia. A nutritional assessment should be performed for all vascular surgical patients, including a history evaluating changes in weight and appetite as well as the patient's functional status (which may impair the ability to obtain or prepare food). Symptoms of nausea, vomiting, dysphagia, constipation, diarrhea, and related gastrointestinal complaints should be assessed, particularly in patients with suspected mesenteric

ischemia. In general, weight loss of more than 5% in 1 month or 10% in 6 months can signify an increased risk for postoperative complications.<sup>82</sup> The physical examination should focus on body habitus and findings of malnutrition such as general weakness, edema, pallor, pressure ulcers, petechiae, ecchymoses, poor skin turgor, fissured tongue, inflamed gums, ulceration of the oral mucosa, brittle hair, and nail abnormalities.

Many laboratory values can be used to assess nutritional status, but serum albumin is the most appropriate. Albumin is the most abundant plasma protein and has a long half-life (18–21 days); it is a marker of chronic protein status and a better evaluation of nutritional status than anthropometric measurements. Serum prealbumin has a shorter half-life and is more sensitive to the short-term response to nutritional support than are assessment tools for chronic malnutrition. Lower preoperative nutritional indices are associated with more severe systemic inflammatory responses after major vascular surgery.<sup>83</sup> Serum hypoalbuminemia (<3.5 g/dL) is an independent predictor of major adverse events and death after major open vascular surgery.<sup>84</sup> More severe hypoalbuminemia (<2.8 g/dL) had an increased odds of mortality (OR 2.5, 95% CI: 1.6–3.8), return to the operating room (OR 1.6, 95% CI: 1.3–2.0), and prolonged length of stay compared to those with normal albumin levels in patients undergoing lower extremity bypass.<sup>85</sup> The association of hypoalbuminemia (<2.4 g/dL) has also been shown to increase 30-day complications as well as short (OR 4.97, 95% CI: 1.36–17.81) and long (OR 2.4, 95% CI: 1.05–5.73) term mortality risk after branched and fenestrated endovascular aortic aneurysm repair.<sup>86</sup>

Despite the nutritional assessment's ability to predict poor outcomes, there are no clear guidelines as to who would benefit from preoperative nutritional support. Preoperative nutritional support can lower postoperative complication rates in patients undergoing intraabdominal surgery, particularly in those with severe malnutrition (albumin <2.1 g/dL).<sup>87</sup> If preoperative nutritional support is offered, up to 25 to 35 kcal/kg per day should be provided, incorporating 1.5 to 2 g/kg per day of protein. A Cochrane evaluation of preoperative nutritional support in patients undergoing gastrointestinal surgery demonstrated that the use of parenteral nutrition significantly reduced postoperative complications.<sup>82</sup> Similar results with oral supplementation or enteral nutrition were not observed, although most experts agree that enteral nutrition is preferred to parenteral because it is safer and more cost-effective. It is recommended that nutritional support be provided for 10 to 14 days before major surgery.<sup>88</sup>

## FRAILTY ASSESSMENT

Evidence is emerging in favor of preoperative strength training and nutritional support to reverse frailty in primary care settings; however, it is unclear which vascular patients would benefit from this prior to surgery.<sup>89</sup> Although not directly related to nutrition, preoperative supervised exercise can reduce postoperative cardiorespiratory and renal complications after elective AAA repair, both open and endovascular.<sup>90</sup>

Many of the classic risk stratification tools have failed to consider the physiologic reserve of elderly patients. This

**BOX 34.1****Preoperative Checklist for Elective Vascular Surgery****For All Patients**

- History
- Physical examination
- Complete blood count
- Serum electrolyte values
- Blood urea nitrogen/creatinine
- Glucose concentration
- Prothrombin time and international normalized ratio
- Electrocardiogram
- Chest radiograph
- Relevant angiographic or cross-sectional imaging
- Blood type and screen
- Informed consent

decreasing physiologic reserve, or “frailty,” which is manifested in functional impairment and multiple comorbidities, has been shown to indicate an inability to recover from major stresses and predict poor outcomes.<sup>91</sup> The concept of frailty represents the increased vulnerability of a patient due to the loss of physical and mental function and the decline of several organ systems. Frailty scores attempt to translate a clinician’s overall risk assessment of a patient (the “eye-ball test”) to an objective measure of risk that can be used in clinical decision making and to engage the patient in a discussion of the risks and benefits of a procedure.

The frailty index, originally derived from the Canadian Study of Health and Aging, has been modified and applied to vascular surgery procedures using 11 variables easily obtained within the NSQIP database to create a modified frailty index. These factors include functional status, diabetes, chronic obstructive pulmonary disease, pneumonia, congestive heart failure, prior myocardial infarction, prior coronary revascularization, hypertension, mental status, prior stroke or transient ischemic attack, and prior peripheral revascularization surgery or amputation. Higher scores on the modified frailty index are associated with higher morbidity and mortality in all surgical specialties, and have been specifically applied to carotid revascularization and aortic aneurysm repair in vascular surgery. More frail patients were almost twice as likely to experience morbidity and mortality after abdominal aortic aneurysm repair, both open and endovascular.<sup>92–94</sup> Frail patients are at higher risk for complications, mortality, and readmission after carotid endarterectomy, but not after carotid artery stenting.<sup>95</sup>

## SUMMARY

A complete preoperative assessment is crucial to minimizing the risk of intervention in vascular surgical patients (Box 34.1). All organ systems need to be evaluated, and risks need to be minimized. Vascular surgery tends to be high risk, and only with appropriate preoperative assessment and risk reduction strategies can we fully protect the vascular surgical patient population.

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

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# Intraoperative Management

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Based on a previous edition chapter by Michael P. Lilly and Tanya R. Flohr

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It is well recognized that the intraoperative management of the patient is a significant determinant of the postoperative course and overall clinical outcome. In light of the frequent associated comorbidity, advanced age, lack of physiologic reserve, complexity of many therapeutic procedures, and other factors, vascular surgical patients can be particularly challenging to manage intraoperatively. The aim of this chapter is to review the important intraoperative considerations the surgical team will face during the conduct of a vascular surgery operation.

## ANESTHESIA

Appropriate anesthesia is tailored to the procedure to allow safe and comfortable interventions that the patient would

otherwise not tolerate. A breakdown of the levels of anesthesia as described by the American Society of Anesthesiologists (ASA) is presented in Table 35.1.<sup>1</sup>

### Anesthesia Techniques and Complications

#### *Local/Regional Anesthesia*

Local anesthetics produce their effects by interfering with nerve conduction through blockade of neuronal sodium channels.<sup>2,3</sup> Most local anesthetics contain an aromatic ring, have a basic pH, and are lipid soluble. They are made soluble in an acidic aqueous vehicle for administration. In tissue, neutral pH is required to achieve neuronal blockade. There are several agents currently available in contemporary practice (Table 35.2).<sup>4</sup>

**TABLE 35.1** Continuum of Depth of Sedation: Levels of Sedation/Analgesia

	Minimal Sedation (Anxiolysis)	Moderate Sedation/Analgesia (Conscious Sedation)	Deep Sedation/Analgesia	General Anesthesia
Responsiveness	Normal response to verbal stimulation	Purposeful response to verbal or tactile stimulation	Purposeful response after repeated or painful stimulation	Unarousable, even with painful stimulation
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	May be impaired

From American Society of Anesthesiologists Committee on Quality Management and Departmental Administration. Continuum of Depth of Sedation: Definition of General Anesthesia and Levels of Sedation/Analgesia. Approved by the ASA House of Delegates on October 13, 1999 and last amended on October 23, 2019. *Anesthesiology*. 2002;96:1004.

**TABLE 35.2** Clinical Features of Individual Local Anesthetic Drugs

Class	Drug	Main Use	Potency <sup>a</sup>	Onset	Duration	Toxicity	Maximal Single Dose	Comments
Esters	Cocaine	Topical	1	slow	30–60 min	Very high	150 mg	Addictive, vasoconstriction, “fight or flight response”
	Benzocaine	Topical	NA	slow	30–60 min	Low	200 mg	Topical only
	Procaine	Infiltration, nerve block	2	fast	30–60 min	Low	1000 mg	Allergic potential
	Chloroprocaine	Infiltration, nerve block	1	fast	30–60 min	Low	1000 mg	No longer available
	Tetracaine	Topical	¼	slow	30–60 min	High	20 mg	No longer available
Amides	Lidocaine	Topical, infiltration, nerve block, epidural	1	fast	1–2 h	Medium	300–500 mg	Versatile agent
	Mepivacaine	Infiltration, nerve block, epidural	1	fast	1–3 h	Medium	400–500 mg	No longer available
	Prilocaine	Infiltration, nerve block, epidural, intravenous regional	1	fast	1–3 h	Low	600 mg	Methemoglobinemia at >600 mg
	Ropivacaine	Infiltration, nerve block, epidural	¼	slow	2–12 h	Medium	20 mg	Enantiomer of bupivacaine
	Bupivacaine	Infiltration, nerve block, epidural	¼	fast	2–12 h	Medium	225 mg	Ventricular arrhythmias, cardiovascular collapse at high doses
	Etidocaine	Infiltration, nerve block, epidural	½	fast	2–12 h	Medium	300–400 mg	No longer available

<sup>a</sup>Relative to lidocaine.

Today, most vascular surgeons use lidocaine, taking advantage of its rapid onset of action; or bupivacaine, because of its long duration of effect.

Ester-containing local anesthetics are cleared by plasma cholinesterase, but amide-based local agents, including lidocaine and bupivacaine, require liver metabolism. Toxic central nervous system effects follow a dose-related progression from vertigo and tinnitus, to anxiety and fear, and subsequently to tremors, seizures, and coma. Benzodiazepines, which increase the seizure threshold related to local anesthetics use, may mask some of the other neurologic signs of local anesthetic toxicity, so particular care is needed in the setting of concomitant

sedation. Direct cardiovascular toxicity is seen at levels exceeding the threshold for seizure and is manifested as arrhythmia and myocardial depression.<sup>5</sup>

### Moderate Sedation

The term *moderate sedation* (often referred to as “conscious sedation”) describes a drug-induced depression of consciousness that facilitates intervention but does not depress the ability of patients to protect their airway. By definition, moderate sedation does not impair independent respiration and normal cardiovascular function and may be administered by non-anesthesiologists who have appropriate training and credentialing.

**TABLE 35.3** Properties of Drugs Commonly Used for Moderate Sedation

Drug	Pharmacologic Class	Pharmacologic Effects	Onset of Action	Duration of Action	Adverse Effects
Midazolam	Benzodiazepine	Sedation Amnesia Anxiolysis	1–5 min, peak in 3–5 min	1–3 h	Hypotension, hypoventilation, decreased tidal volume, increased respiratory rate, apnea, increased upper airway resistance
Diazepam	Benzodiazepine	Sedation Amnesia Anxiolysis	1–5 min	20–60 min	Hypotension, hypoventilation, respiratory depression
Meperidine	Opioid	Sedation Analgesia	5 min, peak in 10 min	2–4 h	Hypoventilation, hypotension, lower seizure threshold, respiratory depression, decreased tidal volume, nausea, vomiting
Propofol	Ultrashort-acting sedative, hypnotic	Sedation Hypnotic	30–60 s	3–10 min	Dose-dependent hypotension, hypoventilation, respiratory depression, pain at injection site
Droperidol	Neuroleptic	Neuroleptic Anxiolytic	30 min	1–4 h	Hypotension, tachycardia, hypoventilation, prolonged QT interval
Fentanyl	Opioid	Sedation Analgesia	<1 min, peak in 5–8 min	30–60 min	Hypoventilation, respiratory depression, decrease in tidal volume

Modified from Lubarsky DA, Candiotti K, Harris E. Understanding modes of moderate sedation during gastrointestinal procedures: a current review of the literature. *J Clin Anesth.* 2007;19:397.

In preparation for moderate sedation, patients should be fasting. A careful history of allergies, adverse reactions, current medications, and conditions recognized to compromise cardiopulmonary function under sedation (e.g., sleep apnea) should be elicited. The facility should have devices and medications for rescue in the event of oversedation. Intraprocedural and postprocedural monitoring should include continuous electrocardiographic and pulse oximetry, in addition to frequent assessment of blood, respiratory rate, and level of consciousness. There are several agents utilized in modern practice (Table 35.3).<sup>6</sup> Reversal agents, naloxone for opiates as well as flumazenil for benzodiazepines, must be immediately available. These receptor antagonists may have durations of action shorter than the agents they are used to block, and therefore continued careful observation of patients after any use of rescue agents is mandated since repeat dosing may be required.

### Regional Anesthesia

*Regional anesthetic* techniques include peripheral nerve blocks, cervical and brachial plexus blocks, spinal anesthesia, and epidural anesthesia. Peripheral nerve blocks can be utilized for extremity and digital procedures with effects lasting well after the operation is complete.

### Spinal and Epidural Anesthesia

*Spinal anesthesia* refers to the injection of medications through the dura directly into the cerebrospinal fluid from lumbar levels. Spinal anesthesia is contraindicated when hemodynamic instability is expected since this technique often produces a sympathetic blockade with some loss of arterial and venous tone. Hypotension associated with spinal anesthesia is treated with fluid resuscitation, Trendelenburg positioning, or inotropic or pressor agents if the patient has underlying heart failure.

Complications of spinal anesthesia include postdural puncture headache, nausea and emesis resulting from unopposed parasympathetic efferents, and respiratory depression particularly in patients with high punctures and chronic obstructive pulmonary disease. Other complications include direct neurologic injury, cauda equina syndrome, arachnoiditis, spinal hematoma, meningitis, and idiopathic cardiovascular collapse. Complications are rare, with the exception of postdural puncture headache which may occur in 25% of patients undergoing spinal anesthesia. The headache may be associated with cranial nerve symptoms such as diplopia, tinnitus, and nausea and is classically relieved by assuming a supine posture. Patients are treated with bed rest, caffeine, hydration, and analgesics.<sup>7,8</sup> This complication may be treated by the administration of an epidural blood patch which is thought to work by sealing the meningeal puncture site.<sup>9–11</sup>

*Epidural anesthesia* refers to the placement of a catheter into the epidural space around the distal thoracic or lumbar spine, frequently with the delivery of larger quantities of anesthetic required for absorption between the spinal ligament and dura (epidural space). A major advantage of epidural anesthesia is the ability to continually deliver post-procedural analgesia via an indwelling catheter. Effective epidural postoperative analgesia may obviate the need for systemically administered opioids and the accompanying risk for respiratory depression, excessive sedation, and gastrointestinal side effects. Epidural anesthetic infusions can be maintained for 3 to 4 days as needed and should not interfere with routine postoperative mobilization.

The safe use of neuraxial anesthesia in the setting of anticoagulant therapy is summarized in Table 35.4.<sup>12</sup>

### General Anesthesia

The term *general anesthesia* refers to a loss of consciousness with the patient being unarousable to painful stimuli. By definition,

**TABLE 35.4** Anticoagulation Management and Neuraxial Anesthetic Intervention

Drug	Waiting Time Before Neuraxial Manipulation	Waiting Time After Neuraxial Manipulation to Restart
Unfractionated heparin, subcutaneous prophylaxis	4 h	>60 min
Intraoperative therapeutic heparinization	2–4 h after the last heparin dose, check partial thromboplastin time	>60 min (Note intravenous anticoagulation should not be continued with neuraxial catheter in place)
Low-molecular-weight heparin	12 h for prophylactic doses 24 h for therapeutic doses	Prophylaxis should be delayed 24 h after neuraxial manipulation and should be limited to once a day dosing Delay prophylaxis until adequate hemostasis is achieved if blood is present during neuraxial manipulation Prophylaxis can be started 2 h after neuraxial catheter removal
Warfarin	When INR <1.4	When INR <1.4
Dabigatran	5 days	6 h
Apixaban	3 days	6 h
Rivaroxaban	3 days	6 h
Prasugrel	7–10 days	6 h
Ticagrelor	5–7 days	6 h
Aspirin, NSAIDs COX-2 inhibitors	Can be continued	Can be continued
Clopidogrel	7 days (if needed before, can perform P2Y12 assay to assess residual antiplatelet activity)	Should be held until after removal

Modified from Horlocker TT, Wedel DJ, Rowlingson JC, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines. 3rd ed. *Reg Anesth Pain Med*. 2010;35:64–101.

patients under general anesthesia cannot protect their airway and, in most cases, require assisted ventilation. Patients receiving general anesthesia often have depressed cardiovascular function and require attention and support by specially trained anesthesiologists.

All of the agents used in general anesthesia can induce peripheral vasodilation and inhibit sympathetic autonomic regulation, leaving the patient with the reduced ability to autoregulate circulation and tissue perfusion. This, plus the lack of surgical stimulation, can lead to hypotension which is frequently noted between the time of anesthesia induction and skin incision. The loss of vasoconstriction in the periphery leads to redistribution of blood flow to the skin, loss of thermoregulation, and a decrease in core temperature.

### Malignant Hyperthermia

Malignant hyperthermia occurs when genetically susceptible individuals are exposed to triggering agents which are usually drugs used during the conduct of a general anesthetic including the use of succinylcholine or a halogenated anesthetic agent. Symptoms include muscle rigidity, tachycardia, hyperthermia, and cardiac arrhythmias. Life-threatening aspects of this include the hypermetabolic condition, hyperthermia, and hyperkalemia.<sup>13</sup>

If malignant hyperthermia is suspected, the surgical procedure should be stopped as soon as possible. Intravenous dantrolene at 2.5 mg/kg can be given through a large-bore IV. Doses can be repeated until decreases in end-tidal CO<sub>2</sub>, heart rate, and muscle rigidity are noted. Dantrolene dosing may need to be increased to 10 mg/kg if muscular contractions persist. The patient should be hyperventilated on 100% oxygen

at greater than 10 L/min to lower end-tidal CO<sub>2</sub> and flush out volatile anesthetics. Activated charcoal filters can be placed in the ventilator circuit and replaced frequently to remove inhaled anesthetic. The patient should be cooled if temperature is greater than 38°C. Metabolic acidosis should be corrected with bicarbonate. Calcium chloride 10 mg/kg or calcium gluconate 30 mg/kg, sodium bicarbonate 1 to 2 mEq/kg IV, 50% glucose 50 mL, and regular insulin 10 units IV can be used to treat hyperkalemia. Refractory hyperkalemia should be treated with albuterol, kayexalate, or dialysis. Calcium channel blockers should be avoided for the treatment of arrhythmias.<sup>13,14</sup>

### Chronic Renal Failure

The number of patients with hemodialysis (HD)-dependent chronic renal failure (CRF) is increasing in parallel to the increasing prevalence of hypertension, diabetes, obesity, and an aging population.<sup>15</sup> Their adjusted all-cause mortality rate is at least 10-fold higher than that of the non-CRF population,<sup>16</sup> with 5-year mortality rates ranging between 39% and 60%, primarily due to cardiovascular disease.<sup>17</sup> Their existing medical problems, such as the increased risk of coronary artery disease and congestive heart failure, complicate their surgical care. Their renal disease, with its resulting volume disturbances, anemia, and electrolyte disturbances, further increase their surgical risk. Not surprisingly, patients with end-stage renal disease (ESRD) undergoing elective vascular surgery have a significantly elevated risk of postoperative complications and death after major vascular surgical operations – particularly in patients over the age of 65.<sup>18</sup> Their perioperative mortality following arterial reconstruction is at least three to four times that of patients without renal failure.<sup>18,19</sup>

The timing of dialysis prior to an operation is a key consideration, given its accompanying volume and electrolyte shifts. The available information suggests that HD on the day before surgery is preferable to correct electrolyte imbalance, uremia, anemia, and excess body fluid.<sup>15</sup>

Special attention must be directed toward intraoperative fluid management since patients may be volume overloaded related to their renal dysfunction, or hypovolemic following a dialysis treatment. Intravenous fluid administration must be considered carefully. A balanced salt solution may be advantageous due to the patient's renal failure-related acidosis, but these solutions contain potassium. Normal saline may lead to hyperchloremia.

The underlying anemia associated with chronic renal failure is generally well tolerated but leads to a risk of compromised oxygen delivery if even relatively small amounts of blood are then lost. Transfusion and its potential risk of volume and potassium overload must be undertaken cautiously.<sup>15</sup>

## INTRAOPERATIVE MONITORING

Continuous monitoring of the patient response to the surgical intervention is critical. This allows both the surgeon and the anesthesiologist to recognize deviations from the expected course and adapt to the changing condition of the patient.

### Electrocardiography

Monitoring of the electrical activity of the heart should be applied throughout the perioperative period in almost all types of interventions. A five-electrode system with four limb leads and a single unipolar precordial lead (generally V<sub>5</sub>) is standard for most vascular procedures. Leads II and V<sub>5</sub> are monitored continuously in most vascular cases. Some evidence suggests that V<sub>3</sub> or V<sub>4</sub> may have greater sensitivity for detection of myocardial ischemia in this setting.<sup>20,21</sup>

### Pulse Oximetry

Pulse oximetry is a noninvasive technique of monitoring oxygen saturation with a probe placed peripherally, often on a finger, earlobe, or toe. Evidence to support its efficacy or impact on outcomes in patients undergoing general anesthesia is scant.<sup>22,23</sup> Nevertheless, its use remains the standard of care.<sup>24</sup>

### Capnography

Continuous monitoring of the end-tidal CO<sub>2</sub> using infrared absorption spectroscopy is the standard of care for the assessment of ventilation during general anesthesia.<sup>24</sup> This information is displayed most commonly as a continuous plot of the partial pressure of CO<sub>2</sub> versus time.

### Arterial Pressure

In clinical practice today, intraarterial pressure is measured with an electromechanical pressure transducer system. The

fluid-filled systems have the added benefit of allowing repeated sampling of arterial blood for laboratory and blood gas analysis. The arterial cannula is commonly inserted into the radial artery. Stenosis, thrombosis, and occlusion of the radial artery are possible complications of cannulation, and ischemia of the hand can result.<sup>25</sup> The ulnar artery is the dominant supply of arterial perfusion to the hand in approximately 90% of people.<sup>26</sup> Assessment of the adequacy of collateralization through the ulnar artery should be assessed and documented before use of the radial artery for monitoring pressure.

### Advanced Hemodynamic Monitoring

#### Central Venous Catheterization

Central venous catheterization can be used to measure central venous pressure (CVP) and to theoretically provide a real-time estimate of intravascular volume and venous return to the right heart. Unfortunately, CVP is affected by many confounding variables which limits its value.<sup>27</sup> CVP correlates well with left ventricular filling pressure only in patients with normal cardiac and pulmonary function. The correlations are further weakened with the use of positive pressure ventilation during surgery and by patient positioning. Absolute values of CVP have little meaning but changes in the parameter with intervention may provide valuable information.

#### Pulmonary Artery Catheterization

Some of the shortcomings of CVP monitoring were overcome by the development of pulmonary artery (PA) catheters. Basic flow-directed balloon-tipped PA catheters can be placed via central venous access and directed through the right atrium and right ventricle into the pulmonary artery. This allows measurement of the pulmonary artery diastolic pressure (PADP). Additionally, the inflation of a balloon at the end of the pulmonary artery catheter to occlude the pulmonary artery briefly allows the measurement of the pulmonary capillary wedge pressure (PCWP), which is a surrogate for the left atrial filling pressure. PA catheters also allow estimation of cardiac output by several different methods and permit sampling of mixed venous blood, which enables calculation of total body oxygen delivery (DO<sub>2</sub>) and total body oxygen consumption (VO<sub>2</sub>).

In spite of the hemodynamic information provided by the use of the pulmonary artery catheter, several large prospective studies have suggested that the use of PA catheters in critically ill patients may offer little objective benefit in survival, and this conclusion has been further supported by meta-analyses.<sup>28–40</sup> In brief, the evidence is insufficient to recommend preoperative hemodynamic optimization for high-risk surgical patients and there is no evidence of benefit for the routine use of PA catheters during general or vascular surgery. Guidelines from both the American College of Cardiology/American Heart Association (ACC/AHA) and the ASA reflect these data and advise against the routine use of PA catheters in vascular surgery but suggest that these devices may be of some benefit in high-risk subsets of patients.<sup>41</sup>

#### Minimally Invasive Hemodynamic Monitoring

Minimally invasive hemodynamic monitoring refers to the several devices that can provide real-time assessment of cardiac

output (CO) without the need of inserting a PA catheter and use either a thermodilution technique or a lithium dilution technique for the CO determination. Transpulmonary thermodilution utilizes an injection of cold fluid into the superior vena cava via a central venous catheter. A thermistor in a main (femoral, axillary, or brachial) arterial branch subsequently measures temperature change over time and a CO calculation is extrapolated.<sup>42</sup> The two commercially available devices using this technique are the PiCCO plus monitor (Pulsion Medical Systems, Munich, Germany) and EV1000/VolumeView monitor (Edwards Lifesciences, Irvine, CA). Lithium dilution is performed with small volume lithium chloride injections via a peripheral or central venous catheter. Lithium concentration is measured by aspirating arterial blood. A lithium-sensitive electrode at the tip of the catheter generates a voltage corresponding with a change in lithium concentration.<sup>43</sup> Lithium dilution hemodynamic monitoring is not accurate in patients treated with lithium or muscle relaxants, since muscle relaxants can incorporate a positively charged quaternary ammonia ion that can trigger the lithium electrode and cause an overestimation of CO. Commercially available lithium dilution hemodynamic monitors include the LidCOplus (LidCO Ltd, Cambridge, UK).

### Transesophageal Echocardiography

Transesophageal echocardiography (TEE) has become a mainstay of the intraoperative management for patients undergoing surgery on the heart and thoracic aorta.<sup>44,45</sup> In particular, TEE can provide direct information on ventricular systolic function.

In spite of the utility of the TEE, there are no published reports to date to demonstrate an outcome-based improvement with TEE.<sup>46–51</sup> This may be related to the generally poor correlation between TEE findings of myocardial ischemia, ECG data, and eventual cardiac outcome. The ACC/AHA 2015 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery suggest that intraoperative or perioperative TEE is reasonable for investigating acute, life-threatening hemodynamic disturbances.<sup>41</sup>

### Spinal Cord Monitoring

The monitoring of spinal nerve function is useful in procedures that involve possible disruption of perfusion to the spinal cord, most commonly through clamping or graft replacement of thoracic aortic segments or placement of thoracic aortic stent grafts which may exclude key intercostal arteries ultimately perfusing the spinal cord (see Ch. 79, Thoracic and Thoracoabdominal Aneurysms: Open Surgical Treatment).

## INFECTION CONTROL

Surgical site infection (SSI) has been estimated to account for at least 25% of all nosocomial infections in hospitals and has been associated with increased mortality, length of hospital stay, and cost.<sup>52–54</sup> Kirkland et al. found that patients with SSI experienced twice the mortality (7.8% vs. 3.5%), a greater

likelihood of requiring ICU care (29% vs. 18%), and a higher incidence of readmission (41% vs. 7%) than matched controls.<sup>55</sup> Risk factors for postoperative surgical site infections in patients undergoing vascular procedures include lower extremity surgical sites, procedures after preoperative hospitalization, the presence of diabetes mellitus, and history of prior coronary or vascular bypass.<sup>56–58</sup>

### Perioperative Antibiotics

The tenets of SSI prophylaxis were established in the 1960s and have been noted in numerous reviews.<sup>59–63</sup> The fundamental requirement for effective SSI prophylaxis is maintenance of an effective concentration of an antibiotic suitable for the probable organisms in tissue at the site and time of incision. The critical role of timing of antibiotic administration is illustrated in the report by Classen et al.<sup>59</sup> When compared with the group who received antibiotics within 2 hours of incision (0.6% incidence of SSI), those who were treated early (>2 hours before incision), perioperatively (within 3 hours after incision), and late (3 to 24 hours after incision) had relative risks for SSI of 6.7, 2.4, and 5.8, respectively.

According to current guidelines, the primary antibiotic agent for SSI prophylaxis during vascular procedures is cefazolin. Vancomycin and clindamycin are appropriate substitutes in the event of β-lactam allergy. Additional recommendations include preoperative dosing 60 minutes before surgical incision, dosing adjustments for body weight, intraoperative redosing to ensure adequate serum and tissue concentrations during the surgical procedure, and a shortened postoperative course of antimicrobials to a single dose or for continuation less than 24 hours.<sup>56,57,64</sup>

The appropriateness of prophylactic antibiotics in percutaneous endovascular interventions has not been determined by prospective randomized controlled trials. Prophylactic antibiotics for the percutaneous placement of stent grafts are recommended. Recommendations are extrapolated to the placement of thoracic, abdominal, and extremity stent grafts.<sup>65–67</sup> Prophylactic antibiotics are not recommended for angiograms, angioplasty, placement of bare metal stents, venous procedures, thrombolysis, or closure devices. In cases of endovascular re-intervention within 7 days of the initial puncture, interventions in the presence of hematoma, procedures lasting more than two hours, procedures performed upon immunosuppressed patients, and interventions in the presence of another intravascular implant, prophylactic antibiotics should be considered.<sup>66–69</sup>

### Skin Preparation

The method used to clean and prepare the skin prior to incision is an area of importance in the prevention of surgical site infections. When hair is to be removed, shaving has been associated with a higher infection rate than clipping.<sup>70–72</sup>

A shower with normal soap taken as close to the beginning of surgery as possible is recommended.<sup>73</sup> Several meta-analyses have concluded that application of an alcohol-based solution to the operative field for cutaneous disinfection is superior to aqueous based prep solutions.<sup>72,73</sup> Care must be taken when

alcohol-based prep solutions are used due to the risk of intraoperative fire in which the trigger is likely to be the use of electrocautery, and flammable alcohol in an oxygen rich environment can serve as the fuel.<sup>74</sup> Chlorhexidine may decrease SSI rates compared with povidone-iodine, and chlorhexidine-isopropyl alcohol likely offers better skin decontamination before clean surgery than povidone-iodine.<sup>75,76</sup>

## MAINTENANCE OF HOMEOSTASIS

Some of the physiologic changes associated with the conduct of an operation and with the anesthetized state such as changes in heart rate, blood pressure, vascular tone, temperature, and glucose metabolism can be maladaptive and lead to increased myocardial oxygen consumption and risk of myocardial infarction, coagulopathy, wound healing problems, increased hospital stay, and mortality. The evidence to manage these problems will be reviewed.

### Anti-Adrenergic Agents

A great deal of research has been performed on the potential role of cardioactive drugs in reducing the cardiac risk associated with major general and vascular surgery.<sup>77</sup> Administration of beta-blockers through the perioperative period has the theoretical benefit of reducing myocardial work through control of heart rate and anti-inotropic actions. The 2014 ACC/AHA Guideline Update for Perioperative Cardiovascular Evaluation for Noncardiac Surgery recommended beta-blocker therapy be continued throughout the perioperative period if patients have been taking it longitudinally and it is well tolerated.<sup>78–85</sup> Vascular surgical patients with intermediate or high risk for myocardial ischemia can be started on beta blockade therapy several days prior to surgery to allow adjustment of the medication.<sup>86,87</sup>

### Maintenance of Normothermia

The combination of anesthesia and surgery leads to major increases in convective heat loss. The loss of peripheral vasoconstriction resulting from anesthesia diverts perfusion from the visceral organs to the extremities and the skin where heat is lost to the environment through thermal radiation. Similar heat loss occurs in large open surgical wounds, especially those of the chest or abdominal cavity where heat loss is augmented by evaporative cooling. For clinical purposes, normothermia is defined as having a core temperature higher than 36°C and lower than 38°C. Mild hypothermia refers to core temperatures between 34°C and 36°C. The physiologic responses of awake humans to mild hypothermia include peripheral sympathetic activation with increased circulating norepinephrine, shivering with increased metabolic rate, oxygen consumption, and mean arterial pressure.<sup>88</sup> In patients undergoing anesthesia with sympathetic blockade, these normal responses to hypothermia are blunted.

Hypothermia is associated with a number of potentially serious complications in surgical patients including wound infection, immune dysfunction, coagulopathy, increased blood

loss, increased transfusion requirements, major adverse cardiac events, and death.<sup>89–97</sup> The most significant concern in patients with coronary heart disease is an increased risk for perioperative myocardial ischemia.<sup>98</sup> Frank and associates assessed myocardial ischemia in the first postoperative day in 100 patients undergoing lower extremity bypass surgery and divided the population into hypothermic (<35°C) and normothermic ( $\geq 35^{\circ}\text{C}$ ) groups on the basis of immediate postoperative body temperature.<sup>98</sup> ECG changes indicative of myocardial ischemia were three times more likely to occur in the hypothermic group (36% vs. 13%), and multivariate analysis showed that temperature was an independent risk factor for myocardial ischemia. A subsequent prospective randomized, controlled trial of supplemental warming of at-risk cardiac patients undergoing vascular, abdominal, and thoracic surgery confirmed that hypothermia is an independent predictor of morbid cardiac events with a relative risk of 2.2.<sup>97</sup> This and other studies have shown a clear relationship between postoperative hypothermia and ventricular tachycardia and atrial fibrillation.<sup>99</sup>

Hypothermia also has a significant effect on coagulation. Many coagulation factors are temperature-sensitive proteases whose activity is reduced by hypothermia. Measurement of this effect *in vivo* is complicated by the fact that the common clinical assays of coagulation (prothrombin time and partial thromboplastin time) are performed at 37°C and thus results do not reflect the impact of actual body temperature at the site of bleeding.<sup>100,101</sup> The clinical impact of mild hypothermia on perioperative bleeding was determined in the report of Schmied estimating that mild hypothermia (1°C) may increase blood loss by 16% and relative risk for transfusion by 22%.<sup>91</sup>

There is also clear evidence of platelet dysfunction with hypothermia.<sup>89,102</sup> Platelet margination occurs with dropping temperature because hypothermia concentrates blood cell volume, induces a change in platelet shape, decreases rate of blood flow, and increases expression of adhesion molecules such as thromboxane A2. The drop in platelet count can be reversed with restoration of normal body temperature.<sup>102–104</sup>

Hypothermia is also a major risk factor for SSI. This effect is mediated by a combination of vasoconstriction at the site of wounding (inoculation) and a generalized effect on immune function. Local vasoconstriction affects the delivery of antibiotics to the wound and may produce relative hypoxia.<sup>94</sup>

A strategy to maintain intraoperative normothermia involves reducing radiant heat loss and providing active warming. Components of this approach include prewarming to reduce the core-to-periphery thermal gradient, passive insulation, active heating (circulating water, forced air, radiant heat), fluid warmers, and airway heating and humidification.<sup>105</sup> The recommended temperature range for the operating room is between 68°F and 75°F.<sup>106</sup>

### Glycemic Control

There is a strong relationship between hyperglycemia and SSI. Latham and associates showed a history of diabetes and postoperative hyperglycemia (defined as glucose >200 mg/dL) were independent risk factors for SSI (OR = 2.76 and 2.02,

respectively).<sup>107</sup> In theory, this association is related to the impact of hyperglycemia on immune function. Specific effects of hyperglycemia may include impaired vasodilatory responses in the wound; changes in expression of adhesion molecules, cytokines, and chemokines; enhanced responses of complement; and depressed neutrophil chemotaxis, phagocytosis, and release of reactive oxygen species. The basic and clinical data supporting these effects have been reviewed.<sup>108,109</sup> In a study of 995 general and vascular surgery patients, Ramos et al. discovered postoperative hyperglycemia increased the risk of postoperative infections by 30% with every 40-point increase from normoglycemia (<110 mg/dL).<sup>110</sup>

There is substantial evidence that aggressive therapy to maintain normoglycemia can have a beneficial effect on mortality in surgical patients. Van den Berghe and colleagues compared routine glycemic management to intensive glycemic control.<sup>111</sup> The intensive-treatment group was managed with insulin infusion to maintain blood glucose between 80 and 110 mg/dL. Overall ICU mortality was 8% with conventional care and 4.6% with intensive management ( $P < 0.04$ ). The greatest difference in mortality was seen in patients who required more than 5 days of ICU care (10.6 vs. 20.2%,  $P < 0.005$ ). Similar substantial differences were noted in the rates of in-hospital mortality, bloodstream infection, and acute renal failure. Others have reported similar findings.<sup>112</sup> More recent studies, however, have shown that there is an increased incidence of hypoglycemia among intensive care patients undergoing strict glycemic control with an increased mortality rate. The Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial randomized 6104 patients within 24 hours of admission to ICU to compare outcomes of patients who were treated with strict glucose control (blood glucose of 81–108 mg/dL) to those assigned to undergo conventional glucose control (180 mg/dL or less). There was a significantly higher mortality rate in the strict glucose control group (27.5%, 829 patients) versus the conventional group (24.9%, 751 patients).<sup>113</sup> In the pursuit of tight glucose control, some patients developed detrimental hypoglycemia. It has been suggested that if the ability to implement the tight limits of normoglycemia are limited by the realities of laboratory and personnel limitations, then more lax and reachable glucose control should be sought.<sup>114</sup>

No specific performance measures have been issued regarding postoperative glycemic control for vascular surgical patients, and there are no randomized controlled trials specifically addressing the monitoring and treatment of hyperglycemia during major vascular surgery. The current guidelines for the perioperative care of patients with peripheral arterial disease is to maintain a blood glucose level of <200 mg/dL.<sup>115</sup>

## ANTICOAGULATION AND ANTIPLATELET THERAPY

Most vascular interventions involve interruption of blood flow and some disruption of the vascular wall, risking local and distant arterial thrombosis. Although the use of systemic anticoagulation and antiplatelet therapy during and after vascular

interventions seems logical, the efficacy of this strategy has not been tested rigorously. There is evidence that systemic anticoagulation is not necessary to prevent local thrombotic complications with aortic aneurysm surgery, although most vascular surgeons use intraoperative anticoagulants. The need for anticoagulation probably varies inversely with the diameter of the arteries and the rate of blood flow.<sup>116</sup>

### Anticoagulation

Anticoagulation is generally initiated just prior to the time of arterial clamping by bolus administration of unfractionated heparin via either an empirical, fixed-dose regimen (5000 units is a common fixed-dose range seen in practice) or a weight-based dosing scheme (75–100 units/kg) (see Ch. 41, Anticoagulant Therapy). The half-life of unfractionated heparin is dose-dependent since clearance has both a rapid saturable phase due to binding to endothelial cells and blood elements as well as a slower first-order elimination phase. The effective half-life in most individuals is 30 to 90 minutes, so repeat dosing (2500 units, or 25–50 units/kg) every 45 to 60 minutes is required to maintain effect.<sup>117–119</sup>

There is considerable variability in the anticoagulation responses to unfractionated heparin, and several studies support monitoring the level of anticoagulation during certain procedures, which is typically accomplished with the activated clotting time (ACT) at the point of care.<sup>120,121</sup> Although the degree of anticoagulation seen with fixed-dose regimens will vary among patients, the clinical impact of such variation in practice is small. Poisik and colleagues measured ACT values during 140 carotid endarterectomies receiving a fixed-dose regimen (5000 units).<sup>122</sup> This regimen in effect delivered weight-based heparin doses of 44 to 116 units/kg and produced ACTs of 175 to 425 seconds with no measurable differences in neurologic outcome or wound hematoma. An ACT longer than 350 seconds appears to be associated with the least risk for ischemic events during percutaneous coronary intervention, and similar values may be appropriate for small-artery interventions in the lower extremities or during carotid stenting.<sup>123</sup> Intraprocedural anticoagulation may also have benefits beyond avoidance of thrombosis in the treated arteries. Some data show a reduction in both fatal and nonfatal periprocedural myocardial infarction after abdominal aneurysm repair when unfractionated heparin was administered systemically at the time of aortic clamping.<sup>124</sup>

There is controversy regarding the benefit of heparin anticoagulation reversal using protamine. Reversal is generally used in shorter duration procedures to speed closure or after intracavitary operations, where the risk of unrecognized hemorrhage can be substantial. Administration of protamine has some risk, with anaphylaxis reported to be 1% or less.<sup>124</sup> Risk factors for adverse reactions to protamine include insulin-dependent diabetes mellitus, a history of vasectomy, allergy to fish products, prior exposure to protamine, and a rapid infusion rate of the medication.<sup>125,126</sup> Some suggest that a single measurement of ACT with reversal for high values (>400 seconds) may be a reasonable approach.<sup>122</sup>

For patients with anti-heparin antibodies or heparin-induced thrombocytopenia, several direct thrombin inhibitors

are available, including hirudin derivatives and argatroban. As recommended in the literature describing its use with percutaneous coronary interventions, anticoagulation with argatroban can start with a bolus of 350 µg/kg administered over 3 to 5 minutes followed by an infusion of 25 µg/kg per minute. For a subtherapeutic ACT, an additional 150 µg/kg/bolus can be given, and the infusion rate can be increased to 30 µg/kg per minute. An ACT should be rechecked in 5 to 10 minutes. For supratherapeutic ACT (>450 seconds), the infusion rate should be decreased to 15 µg/kg per minute. Initial doses in the patient with hepatic impairment should be 0.5 µg/kg per minute.<sup>127</sup> Effective means of argatroban reversal have not been established. Bivalirudin initial bolus dosing is 0.75 mg/kg followed by an immediate infusion of 1.75 mg/kg per hour. ACT should be checked in 3 to 5 minutes and if subtherapeutic, an additional bolus of 0.3 mg/kg should be given if required.<sup>128</sup>

Bivalirudin reversal can be accomplished with recombinant factor VIIa and can be eliminated with hemodialysis. Argatroban and bivalirudin and its derivatives have been compared in populations with heparin-induced thrombocytopenia. The two drugs were equally efficacious with respect to preventing thrombotic events,<sup>129</sup> but argatroban may be advantageous compared to bivalirudin in achieving initial therapeutic anticoagulation goals in patients with suspected or confirmed HIT.<sup>130</sup>

Prothrombin complex concentrate (PCC) is a nonspecific reversal agent derived from plasma composed of vitamin K-dependent coagulation factors II, VII, IX, and X and protein C and S. PCC is approved by the FDA to be used for the reversal of vitamin K antagonist (warfarin)-associated bleeding. Activated prothrombin complex concentrate (aPCC) was developed to treat hemophilia patients and contains activated forms of the coagulation factors II, VII, IX, and X. It is important to note that none of the nonspecific reversal agents are Food and Drug Administration (FDA) approved to reverse target specific anticoagulants with the exception of Praxbind. Hemodialysis is generally only effective for clearance of dabigatran (Table 35.5).<sup>131–133</sup>

## Antiplatelet Therapy

The overwhelming majority of arterial interventions are performed to treat advanced atherosclerosis. Accordingly, virtually every patient undergoing a vascular procedure should be treated with an antiplatelet agent to reduce the incidence of myocardial infarction and ischemic stroke (see Ch. 42, Antiplatelet Agents).<sup>134</sup> The general recommendation for at-risk patients is low-dose aspirin (81 mg) daily. Although clopidogrel is often added empirically as a second antiplatelet agent in many patients, there is little evidence to support the benefit of this agent in low-risk patients who can tolerate aspirin.<sup>135</sup> On the other hand, clopidogrel has an important role together with aspirin in enhancing the patency of percutaneous coronary interventions. In general, dual antiplatelet therapy is recommended for a minimum of 1 month after antiplacement of a bare-metal stent and for a minimum of 12 months after the use of a drug-eluting stent.<sup>136</sup> These recommendations are based on the theoretical time required for endothelialization of the stent. The significant risk for stent thrombosis and fatal

myocardial infarction with premature discontinuance of dual antiplatelet therapy has prompted the publication of the ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery and the Joint Advisory on Prevention of Premature Discontinuation of Dual Antiplatelet Therapy in Patients with Coronary Artery Stents.<sup>136–138</sup> These guidelines suggest delay of elective surgical procedures associated with significant risk for periprocedural bleeding until the appropriate course of dual antiplatelet therapy has been completed and continuation of aspirin throughout the perioperative period in any cases requiring major intervention for which clopidogrel must be discontinued. Naturally, these considerations play a large part in decision making regarding the role of coronary intervention as a risk reduction strategy for high-risk cardiac patients needing urgent vascular interventions since any reduction in cardiac risk achieved by a cardiac intervention must be weighed against the risk of bleeding associated with the mandatory dual antiplatelet therapy.

The risk of bleeding complications with vascular procedures performed on patients treated with aspirin is measurable but small.<sup>139</sup> Neilipovitz and associates estimated that continuation of aspirin through the perioperative period would reduce periprocedural mortality from 2.78% to 2.05% with an associated 2.46% increase in bleeding complications.<sup>140</sup> The 2012 ACCP guidelines on Perioperative Management of Antithrombotic Therapy recommend continuing aspirin in the perioperative period for patients at high cardiovascular risk.<sup>141</sup>

Bleeding during surgery in patients treated with both aspirin and clopidogrel can be a significant problem. Periprocedural clopidogrel has been reported to increase the risk of intraoperative bleeding, as well as the risk of reoperation (OR = 5.1 and 6.9, respectively).<sup>142–144</sup> Like aspirin, clopidogrel must be discontinued for 5 to 7 days for complete resolution of its effect.<sup>145</sup> Most vascular surgeons discontinue clopidogrel in preparation for major open operations. If significant diffuse, punctate platelet-type bleeding occurs intraoperatively, platelet transfusion is often administered. However, there are no real clinical data to support the efficacy of platelet transfusion in this setting.<sup>142</sup>

## Intraoperative Thrombolysis

Although intraoperative fibrinolysis as an adjunct to mechanical thrombectomy in patients with acute limb ischemia was originally reported in the 1980s and has been widely adopted, there are no systematic data to support the optimal dose ranges for specific agents in this application (see Ch. 43, Thrombolytic Therapy).<sup>146–159</sup> Consensus recommendations for intraoperative dosing from the Working Party on Thrombolysis in the Management of Limb Ischemia are available.<sup>159–160</sup> Although surgical site bleeding may not be an issue, the risk for potentially fatal intracranial hemorrhage is real, and rates ranged from 1.2% to 2.1% in the STILE and TOPAS trials.<sup>161,162</sup> Intracranial hemorrhage may be difficult to detect intraoperatively and special caution is thus warranted. Recombinant tissue plasminogen activator (rt-PA) is the most commonly used agent and is typically administered as a catheter-directed bolus into the thrombus often followed by a continuous transcatheter infusion at rates of 1–2 mg/h until lysis of the thrombus

**TABLE 35.5** Target-Specific Anticoagulants

Agent (generic, Trade name)	Mechanism	Half Life	Metabolism	Coagulation Assay	Nonspecific Reversal	Specific Reversal Agents
Dabigatran <b>Pradaxa</b>	Direct thrombin inhibitor Blocks fibrinogen → fibrin	12–17 h	85% renal excretion	Prolonged thrombin time (TT) Prolonged ecarin clotting time (ECT) Range of effect on activated partial thromboplastin time (aPTT)	Hemodialysis is effective Activated charcoal Prothrombin complex concentrates (PCC, KCentra) not effective Recombinant factor VIIa (rFVIIa, Novoseven) effective Activated prothrombin complex concentrate (aPCC, FEIBA) effective	<b>Anti-Dabi-Fab</b> (Idarucizumab/Praxbind)—Humanized monoclonal antibody fragment 5 g IV <b>FDA approved</b> <b>PER977</b> (Aripazine/Ciraparantag)—binds Xa and IIa Phase 2 clinical trials
Rivaroxaban <b>Xarelto</b>	Factor Xa inhibitor Blocks prothrombin → thrombin	5–9 h	66% renal excretion 33% hepatic excretion	Anti-factor Xa activity assay May elevate prothrombin time (PT) Prolonged aPTT	Hemodialysis is not effective Activated charcoal 4 factor PCC (KCentra) is effective, 50 units/kg (max 5000 units) aPCC (FEIBA) effective, 8–25 units/kg	<b>PRT064445</b> (Andexanet Alfa/AndexXa)—binds to Xa inhibitor site Phase 3 clinical trials <b>PER977</b> (Aripazine/Ciraparantag)—binds Xa and IIa Phase 2 clinical trials
Apixaban <b>Eliquis</b>	Factor Xa inhibitor Blocks prothrombin → thrombin	7–14 h	66% hepatic excretion 33% renal excretion	Anti-factor Xa activity assay Prolonged aPTT	Hemodialysis is not effective Activated charcoal 4 factor PCC (KCentra) is effective, 50 units/kg (max 5000 units) aPCC (FEIBA) effective, 8–25 units/kg	<b>PRT064445</b> (Andexanet Alfa/AndexXa)—binds to Xa inhibitor site Phase 3 clinical trials <b>PER977</b> (Aripazine/Ciraparantag)—binds Xa and IIa Phase 2 clinical trials
Fondaparinux <b>Arixtra</b>	Binds to antithrombin III and causes neutralization of Factor Xa	17–21 h	renal	Anti-factor Xa activity assay	Hemodialysis is not effective rFVIIa, Novoseven, 90 µg/kg aPCC (FEIBA) effective, 8–25 units/kg	None

Modified from Hu TY, Vaidya VR, Asirvatham SJ. Reversing anticoagulant effects of novel oral anticoagulants: role of ciraparantag, andexanet alfa and idarucizumab. *Vasc Health Risk Manag*. 2016;12:35–44.

is confirmed. Generally, rt-PA infusions are only continued 12 to 48 hours until the presence of the thrombus can be re-evaluated angiographically.

## CONTROL OF BLOOD LOSS AND TRANSFUSION

### Compensatory Responses to Anemia and Blood Loss

The initial physiologic responses to anemia are an increased stroke volume as a result of decreased impedance to ventricular ejection secondary to reduced blood viscosity and increased venous return because of reduced peripheral vascular resistance.

Data from humans undergoing clinical hemodilution for surgery and from studies of anemic patients who were not transfused for religious reasons suggest that healthy individuals can survive blood loss that reduces the hemoglobin concentration to 5 to 6 g/dL.<sup>163–167</sup> However, these mechanisms depend on maintenance of adequate volume resuscitation in the setting of active bleeding and result in increases in myocardial work and oxygen demand that may be poorly tolerated by vascular patients with significant coronary artery disease.

### Risks Associated with Allogenic Transfusion

#### Noninfection-Related

Allogeneic transfusion exposes the recipient to a variety of cellular, lipid, and protein antigens that can evoke a wide range

of immune-mediated adverse events, including anaphylaxis, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), and both acute and delayed hemolytic reactions. The leading causes of transfusion-related mortality are TRALI, fatal hemolytic transfusion reactions, and transfusion associated sepsis (TAS).<sup>168–170</sup>

TRALI is an acute respiratory distress syndrome characterized by noncardiogenic pulmonary edema and hypoxia occurring within 6 hours of transfusion.<sup>170–172</sup> It is defined as the development of acute hypoxemia and bilateral infiltrates on chest radiograph without pulmonary vascular overload. The risk of TRALI is highest after the infusion of plasma and platelets, but because the transfusion of packed red blood cells is more common, the majority of TRALI cases occur after the transfusion of red cells. The estimated incidence is 1.12% per unit transfused and in at-risk populations, the incidence may be as high as 8%. The mortality rate ranges from 5% to 45%.<sup>173</sup> Treatment is supportive with cessation of transfusion and respiratory support with lung protective mechanical ventilation if indicated (see Ch. 45, Systemic Complications: Respiratory).

Transfusion-associated circulatory overload (TACO) is a common transfusion reaction in patients typically receiving a large volume of blood products. However, patients receiving less than a unit of blood have been reported to have developed TACO suggesting its etiology is more complex than simple volume overload.<sup>174</sup> TACO complicates 1% to 8% of transfusions. Cardiopulmonary dysfunction with TACO is characterized by hydrostatic pulmonary edema in the presence of increased pulmonary artery and left atrial pressures and it often occurs in patients with a history of left ventricular failure. This syndrome is also diagnosed within 6 hours of transfusion. Clinical symptoms include acute respiratory distress, tachycardia, increased blood pressure, acute or worsening pulmonary edema, jugular venous distention, and other signs of positive fluid balance.<sup>169</sup> The chest radiograph will also reveal bilateral infiltrates. Elevated brain natriuretic peptide has a positive predictive value of up to 78%.<sup>175</sup> Treatment includes providing telemetry monitoring, supplemental oxygen, elevating the head of the bed, noninvasive positive pressure ventilation, diuresis, vasodilation with nitrates to reduce preload especially if hypertensive, and renal replacement therapy if indicated.<sup>176,177</sup>

Fatal hemolytic transfusion reactions caused by the infusion of ABO-incompatible blood occur at an estimated incidence of 1 in 1,000,000 and are most commonly due to preventable human error.<sup>178</sup> Acute hemolytic transfusion reactions may be difficult to identify intraoperatively and should be suspected in the event of circulatory decompensation or acute coagulopathy. Management of anaphylaxis intraoperatively involves maintenance of the airway and oxygenation, aggressive fluid resuscitation, and administration of pressors (epinephrine and vasopressin).<sup>179</sup>

Infusion of allogeneic leukocytes may cause several immunologic effects, including alloimmunization-related febrile nonhemolytic transfusion reaction (FNHTR), graft-versus-host disease, and immunomodulation. FNHTR frequency is unknown with a great deal of variability in the rates reported; however, the risk associated is increased with platelet transfusion (with some groups reporting over 20%) as compared to

RBC transfusion. The median rates for FNHTR are 4.6% for platelets and 0.33% for RBCs.<sup>180</sup> These immunologic reactions have been attributed to leukocytes either directly via infusion of intact immunologically competent allogeneic leukocytes or indirectly as a result of infusion of biologically active substances released from leukocytes during storage. These latter substances include histamine, eosinophil cationic protein, myeloperoxidase, plasminogen activator inhibitor-1, and proinflammatory cytokines and chemokines, including interleukin-1, tumor necrosis factor, and interleukin-6.

The downregulation of immune system responses after transfusion has been referred to as transfusion-related immunomodulation (TRIM). Immunotolerance has long been recognized in the setting of renal transplantation with increased transplant survival in recipients who had received multiple previous allogeneic transfusions.<sup>181,182</sup> TRIM has been invoked as the cause of several other deleterious conditions associated with allogeneic transfusion, including an increased rate of recurrence of solid tumors, increased nosocomial infections, and increased mortality.<sup>183–185</sup>

Leukocyte reduction has been shown to decrease the incidence of these immunologic complications of allogenic blood transfusion, as well as reduce transmission of cytomegalovirus in populations at high risk.<sup>186,187</sup> Based on the data available, several countries have adopted universal leukocyte reduction programs for all blood transfusions, and data suggest that such an approach can decrease fever, mortality, and antibiotic use in at-risk patients.<sup>188</sup> There is evidence that the use of leukocyte-depleted blood transfusion may have particular benefit in surgical patients, such as a decrease in the risk for multiple organ system failure and shorter length of stay.<sup>188–191</sup> The impact of leukocyte depletion on the incidence of postoperative infection is less clear and remains controversial.<sup>192,193</sup>

Leukocyte reduction may also have a beneficial impact on a number of changes that affect RBCs during storage, collectively referred to as the “RBC storage lesion.”<sup>194–197</sup> Such changes include a decrease in RBC survival, morphologic alterations, increased osmotic fragility, loss of deformability, conversion of hemoglobin to methemoglobin, and depletion of 2,3-diphosphoglycerate with a resultant decrease in oxygen-carrying capacity and an increase in oxygen affinity.<sup>198,199</sup> There has been a great deal of controversy regarding the potential detrimental effect of RBC storage lesions on the value of RBC transfusion and on the outcomes of patients receiving transfusion. Several small observational studies in patients after trauma or with sepsis have suggested that transfusion of “old blood” (stored between 17 and 25 days) is associated with a greater risk for complications than is transfusion of “fresh blood.”<sup>200–203</sup> Large prospective studies will be required to determine the validity of these retrospective observations, which if true, clearly have profound implications for the current practice of blood banking and maintenance of the blood supply.

### Infection Related

The greatest risk for transfusion-associated transmission of disease arises from bacterial contamination of platelets.<sup>204</sup> Platelet packs are an ideal culture medium for small inocula of bacteria

because the protein-rich plasma may be stored for up to 5 days at 20°C to 24°C. The frequency of bacterial contamination of platelets may be as high as 1 in 1000 or 2000. Bacterial contamination of RBC units is much lower with an estimated rate of less than 1 in 1,000,000. The most common organism in RBC bacterial contamination is *Yersinia enterocolitica*, which carries a mortality rate of 60% and is often fatal in less than 24 hours.<sup>204</sup>

The combination of donor screening programs and nucleic acid testing has progressively lowered the rate of transmission of lipid-encapsulated viruses such as human immunodeficiency virus and hepatitis C to less than 1 in 1,000,000, rates similar to those of major acute hemolytic transfusion reactions.<sup>205</sup> Transmission rates of hepatitis B virus are somewhat higher at about 1 in 50,000 to 150,000.<sup>191</sup> Other infectious agents can also be transmitted through blood products, but rates of transmission in the United States are extremely low. Included in this category are hepatitis D, hepatitis A, hepatitis E, syphilis, leishmaniasis, Lyme disease, brucellosis, parvovirus B19, tick-borne encephalitis virus, Colorado tick fever virus, West Nile virus, and human herpesviruses, as well as parasitic diseases (e.g., malaria, babesiosis, toxoplasmosis, and Chagas disease). Certain diseases are transmitted by transfused leukocytes, including Epstein–Barr virus, human T-lymphotropic virus type I, and cytomegalovirus.

## Transfusion Triggers

Although the benefit of replenishment of RBC volume through transfusion in anemic patients seems intuitive, the data regarding the impact of RBC transfusion on morbidity and mortality in vascular surgical patients are incomplete. There is a lack of clarified threshold for transfusion of RBCs in either critically ill or postsurgical patients.<sup>206–209</sup> The data from patients who refused transfusion would indicate that most patients can tolerate a postoperative hemoglobin concentration of 7.1 to 8.0 g/dL or lower without mortality.<sup>206–208</sup> In contrast, Carson and coworkers demonstrated a clear relationship between mortality and the degree of anemia in the postoperative period, with a 2.5-fold increase in the odds of death for each gram decrease in hemoglobin below 8.0 g/dL.<sup>210</sup>

## Transfusion Strategies

Given the considerable risks associated with allogenic blood transfusion (ABT), several proactive strategies have been developed to reduce or replace the need for transfusion. Key components common to all approaches focus on limiting blood loss and include selection of the proper procedure, meticulous surgical hemostasis, limited phlebotomy, maintenance of normothermia, aggressive management of coagulopathy, and careful resuscitation.<sup>211–212</sup>

Preoperative treatment with erythropoietin may be helpful in anemic patients, as has been demonstrated in elective orthopedic surgery.<sup>213–216</sup> Unfortunately, the frequent clinical urgency associated with the life- and limb-threatening conditions treated in vascular surgery patients makes such a time-consuming approach impractical.

Other strategies involve autogenous transfusion via a number of different techniques. There are three main methods: preoperative autologous blood donation (PAD), acute normovolemic hemodilution (ANH), and intraoperative autologous blood recovery and transfusion (IAT). The basic concept of PAD is that the patient can donate sufficient RBC units to meet the expected perioperative need preoperatively and reconstitute the lost RBC mass before the planned surgery. The use of PAD increased rapidly in the late 1980s and early 1990s but has subsequently declined.<sup>217–221</sup>

Acute normovolemic hemodilution involves removal of whole blood from the patient immediately before surgery with maintenance of normovolemia by infusion of crystalloid or colloid solutions with later reinfusion of the collected blood as needed. ANH increases the demands on the anesthesia team intraoperatively and is not well suited to many vascular patients with baseline anemia and incidence of coronary artery disease. However, there is evidence of potential benefit of ANH combined with IAT in several reports of patients treated for AAA.<sup>222,223</sup>

Intraoperative autologous transfusion (IAT) uses one of several commercially available devices to collect, wash, and concentrate RBCs shed during surgery. The *in vivo* survival of recovered RBCs is similar to that of allogeneic RBCs.<sup>224</sup> Two recent meta-analyses support the conclusion that IAT reduces ABT in the periprocedural period in patients undergoing AAA repair, although a previous meta-analysis suggested no clear benefit.<sup>225–228</sup> Use of IAT is common practice for open infrarenal AAA repair and routine for thoracoabdominal aortic surgery in most centers today.

## VENOUS THROMBOEMBOLIC PROPHYLAXIS

Surgery is a major risk factor for the development of venous thromboembolic disease (VTE). Moreover, vascular surgery patients often have other well-recognized VTE risk factors including advanced age, decreased mobility, cardiac disease, obesity, and smoking (see Ch. 147, Venous Thromboembolic Disease: Mechanical and Pharmacologic Prophylaxis). However, vascular surgery in many ways reduces the risk for VTE. Most vascular patients are treated with antiplatelet agents and virtually all receive full therapeutic anticoagulation during intervention. Postoperatively, some are treated with systemic anticoagulation. VTE prophylaxis has been the subject of call to action by the Surgeon General and was a major component of the Surgical Care Improvement Project (SCIP) and is included in several schemes of value-based reimbursement.<sup>229</sup>

## SPECIAL INTRAOPERATIVE TECHNIQUES

### Laser Safety

Laser energy is applied in the field of vascular surgery in applications ranging from management of varicose veins and endovascular limb revascularization to fenestration of grafts.

Unintended exposure to the laser light is to be avoided by labeling all entrances to the operating room where the laser is in use with regulation laser signs. Doors and windows should be covered. Only authorized individuals who are familiar with laser safety should be in the room. Appropriate laser safety eyewear to filter out the hazardous light wavelength must be worn by all in the room, including the patient.

## Tourniquet Use

The use of a pneumatic tourniquet in Orthopedics is routine and generally avoided in vascular surgery. However, it can be a useful adjunct to the conduct of an operation in the appropriate circumstances. As early as 1980, the use of a tourniquet was suggested to provide a bloodless field for the performance of a distal bypass.<sup>230</sup> Advantages suggested included the fact that clamps need not be applied to the target vessels in the setting of heavy calcification, thereby avoiding injury to the vessel wall. Additionally, a shorter length of the vessel need be dissected free from surrounding tissue. This technique may also help shorten operative duration.<sup>230–235</sup>

The safe application of the tourniquet requires some familiarity with the technique. In general, a 10 cm wide cuff can be applied to an arm, and a 15 cm cuff applied to a thigh. The skin should be well padded. A single use sterile tourniquet can be applied in the surgical field after the extremity has been prepped and draped. Inflation of the cuff has been recommended to be 200–250 mm Hg for the arm and 250–300 mm Hg for the leg.<sup>236,237</sup> The tourniquet should be inflated promptly to prevent venous congestion of the extremity during the time of inflation when venous pressure is exceeded, yet arterial inflow has not been occluded. Inflation time should be minimized, and never more than three hours.<sup>236,238</sup> In the setting of a vascular procedure it is logical that the heparin be administered and allowed to circulate prior to inflating the tourniquet. Compartment syndrome, rhabdomyolysis, and pulmonary emboli are rare complications of tourniquet use.<sup>236</sup>

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# Postoperative Management

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## INTRODUCTION

Complex postoperative care in vascular patients is multi-dimensional and continues well beyond the patient's hospital stay. Cardiac risk stratification preoperatively in the vascular surgical patient will help predict the level of intensity of monitoring required for the postoperative period (see Ch. 34, Preoperative Evaluation and Management). A simple revised Cardiac Risk (MACE) rate: if >3 factors are present using the RCRI, invasive hemodynamic monitoring intraoperatively and postoperatively should be strongly considered.<sup>1</sup> In fact, the type of operation ultimately may need to be simplified or altogether avoided in a patient with very high cardiac risk. As vascular surgeons are tasked with troubleshooting multiple organ systems simultaneously, this chapter is designed to discuss the management of the patients in the early postoperative period.

## ADMISSION TO THE INTENSIVE CARE UNIT AND HIGH-DEPENDENCY STEP-DOWN UNIT

Factors that have been identified as predictors for ICU level of stay after major vascular surgery include advanced age, presence of chronic obstructive pulmonary disease (COPD), intraoperative blood loss >500 cc, operative time over 5 hours, and juxtarenal disease.<sup>2</sup> Other predictors validated in retrospective studies of vascular patients include severe coronary artery disease, defined as an ejection fraction of less than 40%, congestive heart failure, or New York Heart Association class III or IV angina.<sup>3</sup> In addition, special consideration for postoperative ICU should include patients with dialysis dependence that may require continuous renal replacement therapy, ventilatory

support, spinal drain management, and ongoing transfusion requirements. Unexpected hemodynamic lability during the operative procedure should trigger consideration for a move to the ICU or PACU overnight setting for careful monitoring and treatment of blood pressure.

Step-down units with cardiac monitoring and improved patient:nursing ratios are commonly utilized in vascular surgery.<sup>3,4</sup> Cost-effectiveness is also a consideration (intensivist billing results in an ICU overnight stay that is nearly twice as much as a night on a regular nursing floor) and studies have published results displaying equivalent outcomes in post-aortic surgery patients in step-down settings with cardiac monitoring and 2:1 patient to nurse ratios.<sup>5</sup>

## HEMODYNAMIC AND PRESSURE MONITORING

Careful physiologic monitoring is crucial for the optimal care of vascular patients. Patients with normal hemodynamic parameters may concurrently have inadequate organ perfusion.<sup>6</sup> Indicators of organ perfusion are used to guide resuscitation; these include but are not limited to blood pressure, heart rate, central venous pressure (CVP), pulmonary capillary wedge pressure, cardiac output, urine output, blood lactate concentration, tissue carbon dioxide levels, base deficit, mixed venous oxygen levels, and mixed venous carbon dioxide levels.<sup>7-9</sup> Newer devices are becoming available that can non-invasively trend multiple cardiac hemodynamic parameters (cardiac output, stroke volume, systemic vascular resistance, mean arterial pressure) (e.g. ClearSight system, see Novel Monitoring Devices, below) for patient management without access.<sup>10</sup>

### Central Venous Catheters and Central Venous Pressure

Central venous catheters are used primarily to infuse fluids, administer vasoactive drugs, and assess intravascular volume.<sup>11</sup> However, the use of central venous pressure (CVP) to guide fluid resuscitation does have several limitations. The most common sites for the placement of central venous catheters are the internal jugular veins, subclavian veins, and femoral veins. To measure CVP, internal jugular or subclavian central venous catheters must be positioned with the catheter tip in the distal segment of the superior vena cava. Malposition of the catheter is associated with a potential risk for erosion or perforation of vessel walls, local venous thrombosis, catheter dysfunction, and cranial retrograde injection.<sup>12</sup> CVP measures right atrial pressure, providing an estimation of preload except in patients with COPD or in those with valvular heart disease. Femoral lines are good for resuscitation but not for CVP measurements because of the effects of intraabdominal pressure (IAP) on measurements.

The transducer must be zeroed at the level of the midaxillary line; normal values of CVP are between 6 and 12 mm Hg. In patients being managed with positive pressure ventilation,

CVP should be measured at end-expiration, when pleural pressure in the chest is approximately zero.<sup>13</sup> The addition of positive end-expiratory pressure (PEEP) in a ventilated patient is another important consideration in measuring pressure in the chest. In normal lungs and with low levels of PEEP (between 5 and 8 cm H<sub>2</sub>O), the intrapleural pressure, which affects CVP, is only slightly affected.<sup>13</sup> However, with high levels of PEEP (>12 to 15 cm H<sub>2</sub>O) or with non-compliant lungs, the effects on the CVP measurement are probably unclear.<sup>14</sup> High levels of PEEP lead to a decrease in venous return principally due to an increase in mean airway pressure and intrathoracic pressure. This results in a decrease in cardiac output that is further accentuated by impairment of cardiac filling due to leftward displacement of the interventricular septum in response to the increased pulmonary vascular resistance that occurs from the overdistension of alveoli.<sup>15</sup> If sudden changes in CVP occur, a cardiopulmonary cause such as pneumothorax or cardiac tamponade should be considered.

### Peripheral Arterial Lines

Peripheral arterial catheters are the “gold standard” for measuring blood pressure because they provide real time blood pressure monitoring and allow direct vascular access for blood sampling. Complications include bleeding, hematoma, line-related infection, thrombosis, and rarely, limb ischemia.<sup>16</sup> These complications occur to varying degrees, depending on the cannulation site. The most common site for cannulation is the radial artery, followed by the femoral artery, axillary artery, brachial artery, and less commonly, dorsalis pedis and ulnar arteries. These latter sites should be avoided in vascular patients. The radial and the femoral arteries have similar cannulation complication rates.<sup>17</sup> The most common complication of radial artery cannulation is temporary arterial occlusion, which occurs in approximately 20% (1.5%–35%) of the time. Fortunately, occlusion is usually temporary and rarely causes acute ischemia.<sup>16</sup> In contrast to the radial artery, cannulation of the femoral artery is associated with a higher risk of bleeding (1.58% vs. 0.53%) and pseudoaneurysm formation (0.3% vs. 0.09%), but a lower risk of thromboembolism.<sup>16</sup> The ability of the arterial line to accurately reflect blood pressures requires that the transducer be correctly zeroed and placed at the level of the heart. The standard level is the midpoint of the right atrium, approximately 5 cm below the sternal angle in the midaxillary line. This is also the location where the preload pressure of the heart is determined.<sup>14</sup>

Errors in measurement can occur when the system is not appropriately set up to avoid dampening. The distance of the catheter from the heart, the length and compliance of the tubing, lack of pressure in the pressure bag, and the presence of air bubbles can affect the dampening of the system and thus accuracy of the recorded blood pressure. These variables affect systolic and diastolic pressure proportionately in opposite directions and thus have no net effect on the measurement of mean arterial pressure (MAP). For example, an inadequately set up system will result in excessive resonance resulting in an overestimate of the systolic pressure and

underestimate of the diastolic pressure.<sup>18</sup> For this reason, the measurement of MAP is a more accurate reflection of the actual arterial pressure.

The calculation of MAP can manually be performed with the formula  $MAP = \frac{2}{3}$  diastolic blood pressure +  $\frac{1}{3}$  systolic blood pressure. However, electronic monitoring systems measure MAP as the area under the arterial pulse wave, often averaged over three or more cycles.

## Pulmonary Artery Catheters

Pulmonary artery catheters (PAC) provide measurements of intracardiac pressures, derived parameters related to ventricular performance and cardiovascular status, and information such as mixed venous oxygen saturation that relate to end organ oxygen utilization. Pulmonary artery catheters were initially used to assess cardiac performance and treat patients with acute myocardial infarction (MI); however, their use has declined significantly because several randomized trials have failed to demonstrate a reduction in mortality.<sup>19–21</sup> More recent data have even implicated the use of PACs in increased mortality and morbidity.

Pulmonary artery catheters are typically inserted in patients undergoing complex surgical procedures in which potential cardiopulmonary complications are increased or in the ICU to assist with patient management or diagnosis of poor cardiac performance.<sup>22</sup> The information from PACs such as cardiac output, stroke volume, pulmonary artery pressure and pulmonary wedge pressures, and mixed venous oxygen saturation are utilized to assist with the administration of fluids, blood products, and titration of vasoactive medications.<sup>23,24</sup> Indications for placement include patients with cardiogenic shock, discordant right and left heart failure, severe valvular lesions, and pulmonary hypertension.<sup>24</sup>

Complications of pulmonary artery catheters are related to the establishment of central venous access, the catheterization procedure, and catheter residence. Pulmonary artery catheters may induce arrhythmias, which are usually transient and not life-threatening.<sup>25,26</sup> The presence of a preexisting left bundle branch block is a relative contraindication to its use because its placement can induce a temporary right bundle branch block with a resultant complete heart block.<sup>27,28</sup> Other catheter-related complications include catheter knotting, pulmonary artery rupture, catheter fragmentation, and cardiac rupture secondary to forceful insertion. Long-term placement, more than 72 to 96 hours, can also lead to thrombosis and infection. Death related to PACs occur at 0.02%–1.5%.<sup>28</sup>

## Echocardiography

Echocardiography is considered one of the cardiology's greatest discoveries of the twentieth century. It is a very useful tool as a noninvasive modality for perioperative cardiovascular monitoring and diagnosis. Echocardiography can be used to assess cardiac function by measuring ventricular contractility, chamber size, wall motion, valvular function, and flow.<sup>29,30</sup> There have been no randomized trials to support intraoperative

transesophageal echocardiography (TEE) in noncardiac surgery, although its utility as a diagnostic tool during acute hemodynamic decompensation and hemodynamic monitoring should not be overlooked. TEE can be valuable in the setting of cardiovascular collapse where acute hypovolemia, myocardial infarction, pulmonary embolism, and pericardial tamponade are suspected. TEE-based ischemia monitoring has been demonstrated to be more sensitive than ECG; however, the specificity of transient regional wall motion abnormalities remains unclear.

The use of transesophageal pulse-wave or continuous wave Doppler allows for cardiac output (CO) to be calculated as the product of the velocity-time integral and cross-sectional area. The most common site for measuring stroke volume and CO is the left ventricular outflow tract during mid-systole in the mid-esophageal long-axis view. TEE-guided measurement of CO has been demonstrated to accurately correlate with the PAC-derived thermodilution methods, and is thus an acceptable alternative.<sup>31</sup> However, measurement of changes in preload via TEE is more sensitive than pulmonary artery wedge pressure since it is not affected by confounding factors such as ventricular compliance, positive pressure ventilation, or valvular disease. The use of a modified Bernoulli equation ( $4V^2$ ) also allows for the measurement of intracardiac pressures helpful in the perioperative management of critically ill patients.<sup>32</sup>

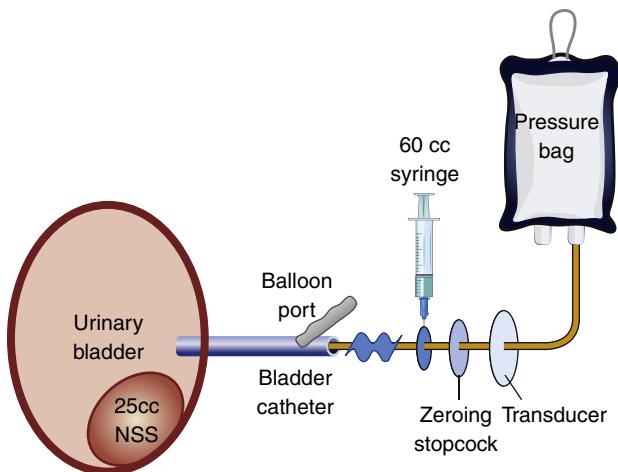
Although TTE has been successfully utilized primarily for intraoperative real time management of patients, there has been increased utilization of trans-thoracic echocardiography (TTE) for a focused cardiac exam to impact perioperative management of patients. This needs to be undertaken by intensivists with significant TTE experience and has been shown to readily identify left ventricular dysfunction, hypovolemia, right ventricular dysfunction and valvular dysfunction. With these diagnoses, besides therapy including volume infusion, appropriate inotropic/vasopressor administration can be initiated or, if appropriate, cardiology consultation obtained.<sup>33</sup>

## Intraabdominal Pressure

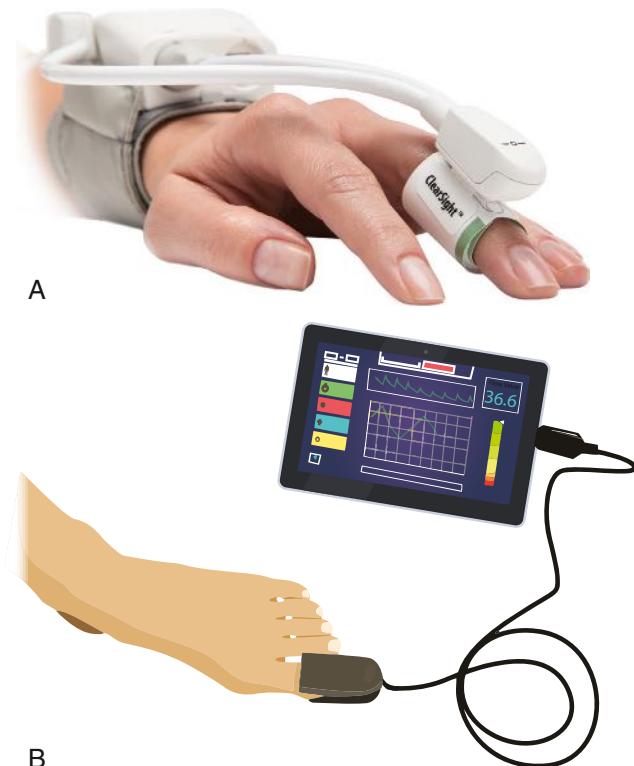
Elevated (<20 mm Hg) intraabdominal pressure (IAP) can lead to multi-organ dysfunction, particularly renal (oliguria), cardiac (decreased cardiac output), and pulmonary (elevated peak airway pressure). Intravesicular measurement of abdominal pressure can be easily performed by placing a catheter in the bladder and instilling 25 to 50 mL of saline. IAP is then measured at end-expiration with the patient in the supine position and the manometer or other pressure-measuring system at the level of the symphysis pubis (Fig. 36.1).<sup>34</sup>

## Novel Monitoring Devices

There are a number of new minimally invasive devices designed to monitor hemodynamics and extremity flow. Since 2016, the “ClearSight” system (Edwards Lifesciences) has helped guide clinical decision making in patients without an arterial line option. The “ClearSight” system is a sophisticated digital blood



**Figure 36.1** Intravesicular Manometry Device. Requires infusing 25 mL of 0.9% normal saline. (From Gavrilovska-Brzanov A, et al. Evaluation of the effects of elevated intra-abdominal pressure on the respiratory mechanics in mechanically ventilated patients. *Maced J Med.* 2013;6(3):261–265.)



**Figure 36.2** (A) ClearSight system. (B) FlowMet-R. (A, From Edwards Lifesciences LLC, Irvine, CA. B, ©2021 Medtronic. All rights reserved. Used with the permission of Medtronic.)

pressure cuff that utilizes plethysmography and additional diagnostic systems to obtain hemodynamic parameters such as mean arterial pressure, stroke volume, and cardiac output.<sup>10</sup> Three separate sizes are available and the devices should be alternated between fingers every 8 hours to improve accuracy (Fig. 36.2A).

The FlowMet-R system (Medtronic) is also applied to the digit like a pulse oximetry sensor and utilizes laser imaging, referred to as “affixed transmission speckle analysis,” to provide two real-time continuous metrics regarding extremity blood

flow (Fig. 36.2B). The device quantifies flow using a numeric scale and the velocity waveform displays a waveform similar to a pulse volume recording (PVR). These real-time data endpoints can be useful for intraprocedural assessment of flow but can also be used for difficult critical care scenarios regarding limb perfusion (e.g. patency of vascular bypass and limb ischemia in patients on ECMO).<sup>35</sup>

## CARDIOVASCULAR MANAGEMENT

### Hypertension

Hypertension is common after vascular surgery and may be caused by hypoxia, hypercapnia, hypervolemia, hypothermia, gastric or bladder distention, agitation, and uncontrolled pain. One of the common causes that should not be overlooked is rebound hypertension due to the failure to restart a patient’s preoperative antihypertensive medications. Uncontrolled hypertension may contribute to increased bleeding from raw surfaces, vascular anastomoses, or suture lines in the immediate postoperative period. A prior history of diastolic hypertension greater than 110 mm Hg is a common predictor of perioperative hypertension.<sup>36</sup> At least 25% of hypertensive patients who undergo noncardiac surgery will develop some degree of myocardial ischemia associated with the induction of anesthesia and during the intraoperative or early postoperative period. When the heart must pump against an increased afterload this increases myocardial oxygen consumption and can potentially cause myocardial ischemia if oxygen demand cannot match supply.

Once correctly identified, treatment of the precipitating factor will often resolve most cases of mildly elevated blood pressure. In general, blood pressure treatment targets should center on systolic blood pressure values 20 mm Hg above or below preoperative pressure.<sup>37</sup> Deviations in MAPs greater than 20% from preoperative values should also be treated.<sup>38,39</sup> In the postoperative period, the ideal antihypertensive agent should have an immediate onset, a short to intermediate duration of action, be easily titratable, and have reliable safety and efficacy in the treatment of perioperative hypertension. In the immediate postoperative period, it is therefore best to titrate the blood pressure with intravenous administration of the drugs. Beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and vasodilator infusions are the most common classes of drugs administered for treatment (see Ch. 14, Hypertension).<sup>40,41</sup>

A “hypertensive crisis” occurs when a patient has a systolic blood pressure of >180 mm Hg, or a diastolic blood pressure that is >110 mm Hg. The term hypertensive crisis can refer to either hypertensive emergencies or urgencies. Hypertensive emergencies occur when there is a severe elevation in blood pressure (>180/110 mm Hg) complicated by evidence of impending or progressive target organ dysfunction that requires immediate treatment to prevent or limit end organ damage. Examples of hypertensive emergencies include acute stroke, hypertension-induced acute renal dysfunction and hypertension associated with unstable angina, acute myocardial infarction, acute coronary heart failure, and acute aortic dissection. Blood pressure should be carefully reduced by 10%–15% (maximum

of 20%) within the first hour towards a goal of 160/100 mm Hg over the next 2–6 hours as tolerated.<sup>42</sup>

Hypertensive urgencies are situations associated with severe elevations in blood pressure, but without progressive target organ dysfunction. Since end organ dysfunction is not present, reduction in pressure can occur over hours to days. Hypertensive patients in these circumstances will often manifest natriuresis, resulting in intravascular fluid depletion requiring the administration of fluid along with antihypertensive medications.<sup>43</sup>

In summary, the treatment goal should be individualized to each patient based on their preoperative blood pressure, the clinical situation, and setting of care. Patients should be carefully monitored for their response to treatment to allow for prompt medication adjustments to ensure paramount safety and efficacy of treatment. Once the patient is stable, the clinician can consider transitioning the patient to an effective oral antihypertensive regimen which can be modified as the patient returns to normal activity.

## Hypotension

Defining hypotension in the perioperative period remains challenging with over 140 different definitions and no international consensus to date to accurately state at which threshold harm may occur. However, postoperative organ dysfunction is associated with both hypotension severity and duration. Untreated and unrecognized postoperative hypotension has been demonstrated to increase the risk of myocardial injury. Other increased risks due to poor perfusion include cerebrovascular events, renal failure and possibly bypass graft thrombosis.

Common causes of hypotension after surgery are residual effects of anesthesia, hypovolemia, cardiac dysfunction, and a diffuse vasodilatory state with or without sepsis. The management strategy should be targeted at the underlying cause with treatment often involving the administration of fluids for hypovolemia and occasionally vasoactive agents. Intravenous fluid should be administered judiciously in a goal-directed manner that considers the Frank–Starling curve to ensure increasing preload will result in an increase in stroke volume. A large pulse pressure variation (>10%–15%) can be indicative of hypovolemia and predictive of volume responsiveness.<sup>44</sup> Surgical bleeding should also be expeditiously excluded or quantified to assess the need for returning the patient to the operating room.<sup>43</sup>

If the hypotension does not respond to fluid resuscitation, cardiac output must be optimized by pharmacologic means. Vasoactive agents such as phenylephrine or dopamine can be given peripherally for a short duration or until central access is obtained. Norepinephrine and vasopressin are significantly more effective at increasing systemic vascular resistance, but should only be given centrally.

In the presence of cardiogenic dysfunction or shock, hypervolemia or use of vasoconstrictors may actually increase the myocardial workload and worsen cardiac output. Inotropic agents with beta agonist activity such as epinephrine or dobutamine are preferred in these situations, but can be more

arrhythmogenic. In the absence of valvular disease, euolemia and a normal sinus rhythm are critical in maintaining adequate cardiac output.<sup>45</sup>

Hypotension with cardiac dysfunction not responsive to inotropic agents needs to be further evaluated for cardiac ischemia. If there is cardiac ischemia or if suspicion of a myocardial infarction exists, cardiac consultation for cardiac catheterization with consideration of mechanical support must be considered. This includes intra-aortic balloon pump, Impella placement, or ECMO may be necessary for hemodynamic support when pharmacologic agents fail.<sup>46</sup> Patients with cardiogenic shock secondary to acute MI have mortality rates higher than 50%.<sup>47</sup> In this scenario, beta-blockers and calcium channel blockers that have a negative inotropic effect are relatively contraindicated in this setting<sup>48</sup> (see Ch. 44, Systemic Complications: Cardiac).

## Arrhythmias

Patients with preexisting structural heart disease are at highest risk for postoperative arrhythmias.<sup>49</sup> Common triggers for postoperative arrhythmias are hypoxia, hypercapnia, acid–base imbalances, electrolyte abnormalities, and myocardial ischemia. Treatment should focus on predisposing factors and the underlying etiology. The goals should be hemodynamic stabilization, control of the ventricular response, and restoration of the baseline rhythm.<sup>49</sup>

## Tachyarrhythmias

The most common tachyarrhythmias are sinus tachycardia, atrial fibrillation (AF), ectopic atrial tachycardia, junctional tachycardia, multifocal atrial tachycardia, atrioventricular (AV) nodal reentry tachycardia, ventricular tachycardia (VT), and ventricular fibrillation. Supraventricular tachyarrhythmias can often be controlled with pharmacological agents that slow conduction through the AV node.<sup>50</sup> Tachyarrhythmias caused by accessory pathways or ventricular in origin are best treated with anti-arrhythmic agents. Supraventricular tachyarrhythmias are common after surgery with an incidence of approximately 4% to 13%.<sup>50,51</sup> Following open AAA repair, the incidence is approximately 3.2%.<sup>50,51</sup> Short bursts of atrial tachycardia often do not require treatment. It is important, however, to investigate and correct any underlying causes such as electrolyte imbalances or pain. For sustained atrial tachyarrhythmia in a hemodynamically stable patient, the etiologies should be investigated, and the rate may be slowed with beta-blockers or calcium channel blockers. Caution should be exercised with these agents, however, when they are used in patients with poor left ventricular function or a history of congestive heart failure. Alternatively, in monitored settings, treatment can be switched to intravenous amiodarone. In stable patients with AV nodal reentrant tachyarrhythmias without Wolff–Parkinson–White syndrome, adenosine (6–12 mg intravenously) can also be used instead of beta-blockers or calcium channel blockers. If a patient is hemodynamically unstable, consideration should be given for immediate electrical cardioversion, regardless of the type of atrial tachyarrhythmia.

Ventricular tachyarrhythmias are also managed according to their duration and hemodynamic consequences. In the presence of coronary artery disease, these rhythms may be ominous. Furthermore, the presence or absence of structural heart disease has prognostic significance<sup>52</sup> and is particularly important when determining treatment strategies in the presences of runs of premature ventricular contractions and nonsustained VT. Prompt evaluation and treatment of predisposing factors such as hypokalemia, hypomagnesemia, hypoxia, and myocardial ischemia are important to prevent sudden death.

Unstable VT is an indication for initiating Advanced Cardiac Life Support (ACLS) with electrical defibrillation. In contrast, hemodynamically stable monomorphic VT can be treated with antiarrhythmics such as intravenous amiodarone, followed by a prompt cardiac evaluation.<sup>52</sup>

In contrast, polymorphic VT and ventricular fibrillation occur most commonly in the setting of acute MI and can rapidly lead to hemodynamic instability. These arrhythmias are also treated with urgent defibrillation and intravenous antiarrhythmics. Polymorphic VT characterized by a gradual change in amplitude and twisting of the QRS complexes around an isoelectric line is known as *torsades de pointes*. Intravenous magnesium is the first line treatment for torsades de pointes to stabilize the myocardium. In cases where the torsades de pointes is refractory to magnesium, positive chronotropic agents such as isoproterenol or temporary overdrive pacing to shorten the QT interval can also be used. Synchronized cardioversion should be performed on a hemodynamically unstable patient who has a pulse, but pulseless torsades should be immediately defibrillated.<sup>53</sup>

### Atrial Fibrillation

Atrial fibrillation (AF) is the most common arrhythmia encountered in the postoperative period affecting 10% of patients undergoing major noncardiothoracic operations.<sup>54,55</sup> Onset is often within the first few postoperative days. AF is associated with increased 30-day postoperative mortality, increased ICU stay, and increased overall hospital length of stay. Common risk factors for the development of AF include advanced age, male gender, valvular heart disease, and previous history of AF.<sup>54</sup> AF can be precipitated by hypokalemia, hypomagnesemia, volume overload, withdrawal of beta-blockers or angiotensin-converting enzyme inhibitors, COPD, obesity and obstructive sleep apnea, and infections, especially pulmonary infections.<sup>54,56,57</sup> A rapid heart rate limits ventricular filling and loss of the atrial component of the cardiac cycle, the “atrial kick” can result in a decrease in left ventricular stroke volume by 20% to 35%.<sup>58</sup> This is especially important in patients with diastolic dysfunction and dilated left ventricles, whose cardiac output is volume-dependent.<sup>59</sup>

Treatment focuses on controlling the heart rate, restoring normal sinus rhythm, and preventing thromboembolic complications.<sup>59</sup> Patients who are hemodynamically unstable, have pulmonary edema, or have ongoing chest pain should undergo urgent synchronized electrical cardioversion of AF. Hemodynamically stable patients should be pharmacologically rate controlled with beta-blockers, amiodarone, digitalis, or calcium

channel blockers. Chemical cardioversion can also be used in hemodynamically stable patients, with one-third of patients converting to normal sinus rhythm with an amiodarone loading alone.<sup>60</sup>

Prior to electrical cardioversion, the patient’s risk for thromboembolic complications must be considered. If AF has been present for longer than 48 hours or for an unknown period, intracardiac thrombus must be excluded.<sup>60</sup> However, in the presence of acute hemodynamic instability, the patient should be electrically converted and once stabilized subsequently monitored for thromboembolic complications. If an intracardiac thrombus cannot be excluded and the patient is hemodynamically stable, the safest course is anticoagulation with unfractionated heparin before cardioversion.<sup>54</sup>

### Bradyarrhythmias

Bradyarrhythmias are not generally a diagnostic challenge and treatment options are straightforward. Those associated with sinus node dysfunction are sinus bradycardia, sinus pause, sinoatrial block, and sinus arrest.<sup>59</sup> Postoperatively, these rhythms are most often due to increased vagal tone and myocardial ischemia. Bradyarrhythmias that are transient and do not result in hemodynamic instability typically do not require treatment. Sustained bradyarrhythmias causing hemodynamic compromise can be treated with antimuscarinic agents such as atropine. If the atropine is not effective, the patient can be started on a dopamine or epinephrine infusion or paced either transcutaneously or with a temporary transvenous pacer.

### Myocardial Infarction

Myocardial infarction (MI) is the most common cause of cardiac complications and mortality in patients with peripheral vascular disease.<sup>61–64</sup> The three modes of detecting clinically meaningful postoperative cardiac ischemia are symptoms, the electrocardiogram (ECG), and evaluation of myocardial enzymes. Symptoms elicited from the patient, often in the form of anginal chest pain, are not a frequent manifestation of postoperative myocardial ischemia but are more commonly found in those with acute coronary syndrome.<sup>65</sup> In the postoperative period, these symptoms can be difficult to distinguish from postoperative pain and are influenced by the concomitant use of analgesia and anesthetics. The presence of ST-segment changes on the ECG may indicate myocardial ischemia or an MI. However, after major vascular surgery, approximately one-third of patients will have ST changes on the ECG in the absence of clinically significant myocardial ischemia.<sup>66</sup> Regardless, the presence of such changes correlates with an approximately 9- to 16-fold increased risk for MI and death.<sup>66</sup> The third method of diagnosing postoperative MI is through the detection of myocardial proteins released into the circulation as a result of myocardial cellular injury. The most common enzymes evaluated are the MB isoenzyme of creatine kinase (CK-MB) and the myocardial-specific cardiac protein troponin I.<sup>67</sup> In vascular surgery patients, increased cardiac troponin I levels in the absence of clinical symptoms have also been demonstrated to be useful in the risk stratification of postoperative

patients for cardiac morbidity.<sup>67</sup> Elevated levels after major vascular surgery are associated with an increased risk for perioperative MI and increased risk for mortality at 6 months.

### ST-Segment Elevation Myocardial Infarction

ST-segment elevation MI (STEMI) is most commonly caused by acute rupture of atherosclerotic plaque and thrombosis of the involved coronary arteries; this is a medical emergency. For this diagnosis to be made, the ECG must show ST-segment elevation of at least 0.1 mV (1 mm) in two consecutive leads.<sup>68</sup> Biochemically, CK-MB levels are elevated 3 to 12 hours after infarction, peak at 24 hours, and can be elevated for 3 days. Cardiac troponin levels can be detected 4 to 12 hours after infarction, peak at 12 to 48 hours, and can remain elevated for 1 week. Treatment involves rapid resuscitation with administration of supplemental oxygen, afterload-reducing agents, antiplatelet therapy, anticoagulation with unfractionated heparin (if at low risk for bleeding), and urgent reperfusion therapy with either fibrinolysis or primary percutaneous coronary intervention (PCI). Postoperatively, fibrinolysis may be relatively contraindicated, but this decision must be individualized to the patient according to the extent of surgery and time interval after the operation. For clinically significant ischemia and patients in cardiogenic shock in the postoperative period, urgent PCI and revascularization are indicated.<sup>69</sup> Emergency coronary artery bypass surgery is reserved for patients who have failed to respond to PCI or fibrinolysis or who have a complication that requires surgery, such as coronary artery dissection.<sup>70</sup> Beta-blockers should also be started immediately to decrease myocardial oxygen demand unless patients are hypotensive or bradycardic, are in congestive heart failure, have advanced AV block, or have reactive airway disease.

### Non-ST-Segment Elevation Myocardial Infarction

Non-ST-segment elevation MI (non-STEMI) is characterized by the presence of biomarkers indicative of myocardial injury in the absence of ST elevation on the ECG. The key difference from STEMI is in this scenario there is myocardial ischemia in the absence of significant coronary obstruction, such as occurs with acute plaque rupture. The myocardial ischemia in this setting is due to a transient reduction in coronary blood flow that causes an imbalance in myocardial oxygen supply and demand, which can easily result from the increased systemic demands in the postoperative period. The patient often presents clinically with shortness of breath and decompensated heart failure. The ECG can demonstrate nonspecific T-wave inversion or ST depression, and an important key to its diagnosis is the presence of circulating biomarkers (CK-MB, troponin I, troponin T) indicative of myocardial cellular necrosis.<sup>70</sup> Mortality risk is directly proportional to troponin levels, or the level of injury.<sup>71</sup>

Treatment is medical and centered on optimizing myocardial oxygen delivery, decreasing myocardial demand, and preventing recurrence of MI and death.<sup>72</sup> Control of postoperative pain and other stimulus of myocardial demand should also be addressed. Treatment can be thought of as the ABCs (acetylsalicylic acid, angiotensin-converting enzyme inhibitor, beta-blockers, and cholesterol lowering (statin therapy).

Administration of unfractionated heparin is also associated with a mortality benefit,<sup>72</sup> but its use must be balanced with the risk of bleeding in the postoperative period. In the setting of ongoing chest pain, the most recent American College of Cardiology/American Heart Association guidelines recommend the use of sublingual nitroglycerin if the systolic blood pressure is higher than 90 mm Hg and the heart rate is not less than 50 beats per minute or more than 100 beats per minute. If further analgesia is needed after nitroglycerin is given, morphine sulfate or meperidine can be used.<sup>72</sup>

## PULMONARY MANAGEMENT

Postoperative pulmonary support is most often indicated for patients who have undergone prolonged procedures that involve the thoracic cavity (thoracoabdominal procedures), significant fluid shifts due to substantial blood loss, and who require extensive pain control. Respiratory insufficiency can be divided into either oxygenation failure or ventilation failure. Oxygenation failure is typically associated with hypoxemia, whereas ventilation failure is associated with hypercapnia due to inadequate CO<sub>2</sub> elimination.<sup>73</sup>

### Ventilatory Support

#### Mechanical Ventilation

Mechanical ventilation is almost universally achieved today by positive pressure ventilation to replace or supplement normal spontaneous ventilation. Oxygenation can be augmented by increasing the fraction of inspired oxygen and controlling airway pressure by increasing the mean alveolar pressure, mean airway pressure, and PEEP. Ventilation is determined by tidal volume and respiratory rate. The major potential disadvantages to positive pressure ventilation are worsening ventilation-to-perfusion mismatch, adverse circulatory effects, and risk of barotrauma and volutrauma.<sup>73</sup>

Patients are ventilated primarily in two modes: controlled and supported. In controlled ventilation, the ventilator initiates and delivers a set amount of tidal volume; in supported mode, the breath is initiated by the patient and supported by the ventilator. Ventilators may deliver either a fixed tidal volume with variable pressure (volume control) or a variable tidal volume at a fixed pressure (pressure control). The combination of these two general modes of ventilation (controlled versus spontaneous) with either of these two settings (volume control versus pressure control) accounts for the majority of modes with which patients are ventilated.<sup>73</sup>

Modern classification of ventilators has become complex in that nomenclature to describe ventilation mode is determined by a combination of the control variable (pressure, volume, or flow), targeting scheme, and breath sequence. The control or target variable is independent of the mode; for example, in pressure-controlled ventilation (PCV) the pressure is the independent variable. The targeting scheme is a feedback design that delivers a specific pattern, the most common of which is set point targeting, where the clinician sets the value and the ventilator attempts to deliver it. For

example, in volume-controlled ventilation (VCV) the set point is tidal volume and flow and in PCV the parameters are inspiratory pressure and inspiratory time. The breath sequence of the ventilator mode refers to whether the breath pattern is mandatory, spontaneous, or both. In controlled spontaneous ventilation (CSV), also known as assist-controlled ventilation, all breaths are spontaneous. During intermittent mandatory ventilation (IMV) spontaneous breaths are permitted in between mandatory breaths, but when the breath is triggered by the patient this is referred to as a “synchronized” mandatory breath. In continuous mandatory ventilation (CMV) all breaths, including those initiated by the patient, are mandatory. Combining the two types of control variable (PC and VC) with the three breath sequences, the five breathing patterns are: VC-CMV, VC-IMV, PC-CMV, PC-IMV, PC-CSV.<sup>73</sup>

Immediate postoperative patients who possess minimal or no respiratory effort benefit most from a controlled mode of ventilation to limit the work of breathing. In addition, a fixed tidal volume and respiratory rate help to ensure consistent ventilation. Selection of pressure vs. volume control depends greatly on the clinical scenario. In PCV, pressure and inspiratory time are preset and the ventilator will cycle into the expiratory phase once airway pressure reaches a predetermined level. Tidal volume cannot be guaranteed because flow and volume become dependent on airway resistance and pulmonary and circuit compliance. An example where a pressure-limiting mode is preferred is in the management of acute respiratory distress syndrome where PC allows for a lung protective strategy that reduces peak airway pressure and the risk for volutrauma.<sup>74</sup> During VCV the ventilator terminates inspiration once a preset volume is delivered. However, because inspiratory time, flow, and VT are preset, an increase in resistance or reduced compliance can substantially increase inspiratory pressure. Fortunately, many volume-cycled ventilators have secondary limits on inspiratory pressure to guard against accidental barotrauma.<sup>75</sup>

Prevention of ventilator-induced lung injury can attenuate multiorgan failure and improve survival. Volutrauma is overdistension-mediated lung injury that is related to the repetitive collapse and re-expansion of alveoli. Barotrauma refers to high inflation pressure-mediated lung injury and is associated with repetitive high peak inflation pressures and underlying lung diseases. In ARDS, shear stresses created from the cyclic opening and closing of atelectatic but recruitable lung units contribute to atelectatic trauma.<sup>75,76</sup> PEEP applied throughout the ventilatory cycle serves to stent alveoli open, which prevents atelectatic trauma and facilitates gas exchange. The ideal level of PEEP is unknown, but an accepted range, depending on the clinical situation, is 5 to 15 cm H<sub>2</sub>O. Mechanical lung injury can also trigger an extensive biological response referred to as biotrauma that is due to the activation of a proinflammatory and proinjurious cytokine cascade. Most importantly, this proinflammatory response promotes extrapulmonary organ injury, predisposing to multiorgan failure that carries increased risk of death<sup>77</sup> (see Ch. 45, Systemic Complications: Respiratory).

## Weaning from Mechanical Ventilation

There are two main phases in the weaning process. The first is “readiness testing” where weaning parameters and clinical assessment are employed to determine if the patient can sustain the progressive withdrawal of mechanical ventilatory support. The second phase is removal of the endotracheal tube, “liberation” from the ventilator.<sup>78,79</sup> Patients should be assessed daily for readiness to be weaned, which can be done only after interruption of sedation.<sup>79</sup> This method has been called “wake up and breathe.” Several randomized trials have revealed that weaning method influences the duration of ventilation.<sup>80–82</sup>

Common approaches to weaning involve the progressive reduction in ventilatory support over time through a protocol via SIMV or pressure support and periods of spontaneous breathing with a T-piece or on low levels of CPAP.<sup>82</sup> Spontaneous breathing trials without progressive withdrawal of ventilatory support may be associated with earlier extubation.<sup>83</sup> With the traditional approach to weaning, patients are switched from a controlled to SIMV or a spontaneous mode of ventilation such as pressure support ventilation. The amount of ventilatory support and PEEP is then decreased according to oxygen saturation, respiratory rate, and tidal volume. If the patient is not ready for weaning, a decrease in tidal volume and an increase in respiratory rate will be noted.<sup>84</sup> When a spontaneous breathing trial is used, patients are allowed to breathe spontaneously with little or no assistance. Most often, patients will be placed on minimal support (pressure support at 5–8 cm H<sub>2</sub>O, PEEP at 5 cm H<sub>2</sub>O) for 30 minutes to 2 hours. In a successful trial, the patient does not demonstrate respiratory distress (respiratory rate >35 for >5 minutes), desaturation (SaO<sub>2</sub> <90% for >30 seconds), increase or decrease in heart rate ( $\pm 20\%$  for >5 minutes), systolic blood pressure higher than 180 mm Hg or lower than 90 mm Hg, or other signs of agitation and distress (paradoxical breathing, use of accessory muscles, diaphoresis).<sup>84</sup>

## Indications for Extubation

Once patients are weaned from the ventilator and have successfully spent a prolonged time with minimal PEEP and on minimal pressure support, they can be assessed for the potential for extubation. All underlying conditions necessitating intubation should be reversed or corrected prior to extubation. Contraindications to extubation are altered mental status (sedation), inability to protect the airway, presence of copious secretions, and lack of a cough reflex. Consideration must also be given to whether the patient was identified as a difficult intubation in order to have the proper equipment (video laryngoscope, fiberoptic) and medical personnel, such as an anesthesiologist, at bedside. Failure of extubation is associated with increased mortality and a need for long-term ventilation.<sup>85</sup> The harm of reintubation must be balanced by the complication associated with prolonged mechanical ventilation. Reintubation rates of 10% to 15% are within the normal range in most ICUs.<sup>86</sup>

## Tracheostomy

A tracheostomy improves patient comfort by reducing the work of breathing required to overcome the resistance of the

endotracheal tube and the upper airway. It also allows for better oral hygiene, secretion management, and the potential for speech. The major disadvantages of a tracheostomy are procedure-related complications, stomal complications, formation of a tracheoinnominate fistula, or a tracheoesophageal fistula. Early tracheostomy within the first week in patients who are thought to require ventilation for more than 10 days facilitates weaning and is associated with a shorter length of stay in the hospital.<sup>87</sup> Jubran et al. found that in patients who required prolonged mechanical ventilation, unassisted breathing through a tracheostomy resulted in shorter median weaning time compared with pressure support.<sup>88</sup> However, in a retrospective observational study after abdominal and thoracoabdominal repair, Diedrich et al. found that, overall, tracheostomy correlated with worse outcomes, but that patients with preexisting COPD who received a tracheostomy had improved survival.<sup>89</sup>

Tracheostomy can be performed by either an open surgical procedure or percutaneous approach. Percutaneous tracheostomy is as safe as open surgical tracheostomy, with the advantage that the patient does not require transport to the operating room. Furthermore, no difference in long-term outcomes between percutaneous and open surgical tracheostomy has been shown.<sup>90</sup> However, percutaneous tracheostomy is relatively contraindicated in high-risk patients who are hypoxic and have high PEEP requirements, are obese with short necks, are coagulopathic, and those with recent (<10 days) anterior cervical spine fixation.<sup>90</sup>

## POSTOPERATIVE BLEEDING

Patients with greater than expected fluid requirements postoperatively must be urgently evaluated for bleeding.<sup>43</sup> The physiologic response to hypovolemia includes tachycardia, hypotension, low CVP, decreased urine output, and signs of peripheral vasoconstriction.<sup>91</sup>

### Surgical Bleeding

An unstable patient with rapidly escalating doses of pressors in the early postoperative phase is bleeding until proven otherwise. The “bloody viscous cycle” with further exhaustion of clotting factors with worsening coagulopathy can lead to more rapid exsanguination. A rapid evaluation before formal laboratory values are obtained can be performed by iSTAT in the PACU or ICU setting (Fig. 36.3). In an unstable patient, it is prudent to activate the operating room while obtaining blood products from the blood bank. In a more stable patient, imaging studies can sometimes be helpful to evaluate the site of bleeding and determine the need for re-exploration.

### Coagulopathy

For a summary of coagulopathy, see Table 36.1. Assessment of the coagulation system by measurement of the aPTT, prothrombin time (expressed as the INR), platelet count, and fibrinogen should be done immediately to guide therapy (see Ch. 39, Disorders of Coagulation: Hemorrhage).



**Figure 36.3** i-STAT. (Abbott, Abbott A, and iSTAT are trademarks of Abbott or its related companies. Reproduced with permission of Abbott, © 2021. All rights reserved.)

**TABLE 36.1** Postoperative Coagulopathy

	Possible Problems	Treatment
Prolonged aPTT and normal INR	Heparin Hemophilia A Hemophilia B Hemophilia C	Protamine Factor VIII Factor IX Factor XI
Normal aPTT and increased INR	Warfarin Vitamin K deficiency Drugs	FFP or vitamin K or prothrombin complex concentrates Vitamin K
Normal aPTT and normal INR	Platelet dysfunction Thrombocytopenia	Platelet transfusion Platelet transfusion
	Hypothermia	Warm patient
Prolonged aPTT and increased INR	Primary fibrinolysis Disseminated intravascular coagulation	Treat underlying cause Cryoprecipitate if fibrinogen <100 mg/dL (<150 to 200 mg/dL in severe bleeding) Tranexamic acid FFP if factors <25% of normal Keep platelets >50 × 10 <sup>9</sup>

aPTT, activated partial thromboplastin time; FFP, fresh frozen plasma; INR, international normalized ratio.

## FLUID AND ELECTROLYTE MANAGEMENT

Fluid administration in the postoperative period must be tailored to the individual patient. Many patients can be treated with maintenance fluids based on a simple weight-based calculation such as the “4-2-1” rule. For example, a 70-kg

man would require 110 mL per hour of crystalloid (40 mL for first 10 kg; 20 mL for second 10 kg; and 50 mL for remaining 50 kg). Titration of crystalloid should be to physiologic endpoints. The most reliable endpoint is urine output in patients with normal renal function based on an indwelling Foley catheter. However, many patients do not require bladder catheterization after surgery and crystalloid infusions should be limited to avoid unnecessary fluid overload. If large volumes of crystalloid solution are administered for resuscitation, it is recommended that a balanced salt solution such as lactated Ringer's solution be given instead of normal saline to reduce the development of iatrogenic hyperchloremic metabolic acidosis.<sup>92</sup> Colloids are commonly used for fluid resuscitation as well due to the theoretical benefit of expanding intravascular volume and their osmotic activity reduces third spacing. However, there appears to be no survival benefit when albumin or other colloid solutions are used in lieu of crystalloid in severely ill patients.<sup>93</sup>

Electrolyte repletion – particularly potassium, magnesium, and phosphate – requires assessment of daily serum chemistry values. Careful attention should be paid to renal insufficiency since these patients will have difficulty clearing potassium. Certain surgeries (e.g. liver resection and aggressive phosphate supplementation) require specific electrolyte repletion and standing orders should be considered for daily repletion protocols. Hyponatremia and hypernatremia are more complex and should be managed very carefully based on the patient's volume status.<sup>94</sup>

## RENAL FAILURE

The greatest predictor for postoperative renal failure is preoperative renal insufficiency as evidenced in several vascular surgery retrospective trials (see Ch. 46, Systemic Complications: Renal). Postoperative management with dopamine has not shown to improve renal outcomes or survival.<sup>95</sup> Fenoldopam (a selective dopamine<sub>1</sub> receptor agonist) also has controversial data supporting its use in small translational research studies.<sup>96,97</sup> Individualized management of renal insufficiency with fluid resuscitation and selective use of loop diuretics is often required in the postoperative setting.

## GENERAL CONSIDERATIONS

### Gastrointestinal Ischemia

Gastrointestinal ischemia is a frequent complication of aortic surgery with an incidence of 2% in elective settings and upwards of 60% in aortic ruptured scenarios<sup>98</sup> (see Ch. 133, Acute Mesenteric Ischemia: Epidemiology, Pathophysiology, Clinical Evaluation, and Management). Previous studies of ruptured aortic aneurysm patients displayed varying degrees of ischemia – graded I to III – with varying treatment options. Clinical findings indicative of intestinal ischemia, which is most frequently colonic ischemia, include new onset abdominal pain and lower GI bleeding. Laboratory and

imaging findings include leukocytosis, anion gap acidosis, expanding free air, pneumatisis intestinalis, or portal venous gas.

Stable patients with endoscopic results suggesting ischemia limited to the mucosa (grade I) may be treated conservatively with hydration and broad-spectrum intravenous antibiotics. However, immediate exploration is warranted in such patients if the condition worsens or hemodynamic instability ensues. Unstable patients with evidence of endoscopic findings of more advanced bowel ischemia (grade II – muscularis layers; grade III – transmural) should undergo urgent surgical exploration to reduce mortality. In selected cases of colon ischemia that has not progressed to gangrene, reimplantation of the inferior mesenteric artery can be considered. In the setting of frank gangrene, the colon should be resected and a colostomy created – a Hartmann's procedure.<sup>98</sup>

### Nutrition

Daily nutrition goals for an ICU patient can be difficult to assess given the critical condition of the patient. Short-term biomarkers like prealbumin can be misleading due to the pro-inflammatory state of most postoperative patients. Hence, daily goals for calories and protein should be followed. Recommended nutrition doses based on guidelines are up to 20 to 25 kcal/kg actual body weight per day in the acute phase of critical illness (72–96 h) and 25 to 30 kcal/kg body weight per day in the recovery phase. Daily protein requirement is 1 g per kg but can be as high as 1.5 g per kg in critically ill trauma (or burn) patients.<sup>99</sup>

The two main routes of administering nutrition in critically ill patients are the enteral route and the parenteral route. As a general rule, the enteral route has the most benefit for the patient. In patients who are unable to eat, enteral nutrition is preferred to parenteral. Feeding should be started within the first 24 to 48 hours of admission to the ICU and advanced toward goal during the next 48 to 72 hours. Enteral feeding can be started through either a gastric tube or small bowel tube in the absence of traditional markers of bowel function (bowel sounds, flatus, or passage of stool). Patients are often challenged with trickle feeding at 10 mL/h to ensure tolerance before increasing rapidly toward goal. Placement of a feeding tube in the proximal small bowel should be considered in patients with inadequate gastric emptying as evidenced by residual gastric volumes in excess of 500 mL.<sup>100</sup>

If early enteral feeding is not feasible, parenteral nutrition should be considered if the anticipated duration of nutritional support will exceed 7 days. Shorter periods of parenteral nutrition (e.g., <5 to 7 days) expose the patient to a variety of vascular access, metabolic, and infectious risks without proven long-term benefit. Even in patients stabilized on parenteral nutrition, periodic efforts should be made to start enteral feeding. However, parenteral nutrition should not be discontinued until enteral nutrition is providing at least 60% of target requirements.<sup>100</sup>

## Pain Management

Pain management in the vascular surgery patient requires a multi-faceted approach given that many vascular patients suffer from pre-existing chronic pain conditions. A complex range of mechanisms including nociceptive, inflammatory, ischemic, and neuropathic pain may all occur. Recognition of the predominant pathophysiological process is essential to ensure the optimal analgesic choice, strategy, and method are selected. Utilization of pre-emptive analgesia, multimodal medications, and regional anesthesia can significantly improve pain control and reduce the development of debilitating chronic pain syndromes.

Uncontrolled pain leads to an increased stress response and activation of the autonomic system that is particularly detrimental in patients with vascular disease and the associated underlying comorbidities, especially cardiac. Neuraxial anesthesia has extensive benefits – reducing the overall opiate requirement, improved gastric emptying, decreasing risk and increasing patient mobility.<sup>101</sup> In addition to vasodilation of the lower extremity from neuraxial anesthesia, patients who are mobilized earlier also can benefit from reduced thrombotic events and pulmonary complications. Considerations regarding the timing of anticoagulation in the setting of regional anesthesia is important to avoid complications associated with bleeding, such as an epidural hematoma. Performance of neuraxial procedures or peripheral nerve blocks, catheter removal, and timing for restarting anticoagulation should follow the recommendations of the American Society of Regional Anesthesia guidelines. For example, LMWH injections should be delayed for 2 hours following spinal needle placement or catheter removal.<sup>102</sup>

## Deep Venous Thrombosis Prophylaxis

All vascular surgery patients should receive DVT prophylaxis in the postoperative setting. Low-molecular-weight heparin has a risk of heparin-induced thrombocytopenia that is much lower than standard unfractionated heparin (0.2% vs 2.6%).<sup>103</sup> Additional measures to reduce DVT include early ambulation and intermittent pneumatic compression. The timing of anti-coagulant initiation postoperatively is controversial. Most of the prior trials initiated unfractionated heparin and LMWH approximately 2 hours postoperatively with a low rate of bleeding.<sup>104</sup> Prophylaxis is generally given until patients become ambulatory and mobile but should be continued for upwards of 30 days in high-risk patients (active cancer, Caprini score >4)<sup>105</sup> (see Ch. 147, Venous Thromboembolic Disease: Mechanical and Pharmacologic Prophylaxis).

## Bridging Postoperative Oral Anticoagulation

Bridging with full-dose anticoagulation in the postoperative period is only necessary for patients that are very high risk for a thromboembolic event. The main two high-risk categories include the patients who have a mechanical mitral valve or an old-model mechanical aortic valve. Preoperatively, these two

patient groups should have oral anticoagulation stopped 4 days before surgery; heparin should be started 2 days before surgery according to published guidelines by the American College of Chest Physicians.<sup>106,107</sup> Postoperatively, heparin should be restarted as soon as possible for these two high-risk groups and overlapped with the oral anticoagulant to ensure adequate anticoagulation. The surgeon must balance the risk of postoperative bleeding with a thromboembolic event such as a stroke.

## Alcohol Withdrawal Syndrome

The typical onset of alcohol withdrawal is 24 to 48 hours after surgery. Symptoms typically peak around the third to fifth postoperative day. Agitation, vomiting, tremors, and nausea can be seen in mild cases with seizures and delirium tremens in severe situations. The revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar) is a 10-item scale for assessing alcohol withdrawal. It can be used frequently in the ICU and is very helpful in guiding treatment for withdrawal symptoms. Scores less than 10 do not require treatment. Scores over 20 require pharmacologic treatment, usually with a benzodiazepine. Scores between 10 and 20 require clinical judgment since this is an intermediate zone. Before pharmacologic treatment is initiated for presumed alcohol withdrawal, hypoxia must be ruled out (hypoxia is the most common cause of confusion and agitation in the postoperative period).<sup>108–110</sup> All patients should also be given daily thiamine and multivitamins to prevent Wernicke–Korsakoff syndrome.

## Sedation and Delirium in the Intensive Care Unit

Postoperative delirium is an important consideration in vascular surgery patients for three reasons: the increased incidence in geriatric patients; variable mode of presentation; and potential gravity of the consequences.<sup>111</sup> Delirium can be seen in 14% to 24% of hospitalized patients and may be as high as 53% in the postoperative phase.<sup>112</sup> According to one of the original descriptions referenced in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), delirium is a “cognitive disturbance of brutal onset, usually occurring in the 24th to 48th hour postoperatively but can be difficult to diagnose based on its fluctuating character and intensity.” Delirium carries added weight in postoperative patients since it is a known predictor for prolonged hospitalization and mortality within 12 months after hospitalization.<sup>117</sup> Hence a basic understanding of delirium and its subtypes is important for vascular surgeons practicing in inpatient hospital settings.

Delirium (or delirium syndrome – “DS”) has three known subtypes. A hyperactive form is seen 25% of the time and can be difficult to distinguish from alcohol withdrawal. A hypoactive – less threatening – form can be seen 25% of the time and can have a metabolic origin. Lastly, a mixed form, which has features of both previously mentioned forms, is seen half of the time.<sup>113</sup>

The confusion assessment method (CAM) is a sensitive (94%–100%) and specific (90%–95%) diagnostic tool for

### Confusion Assessment Method (CAM)

Short form

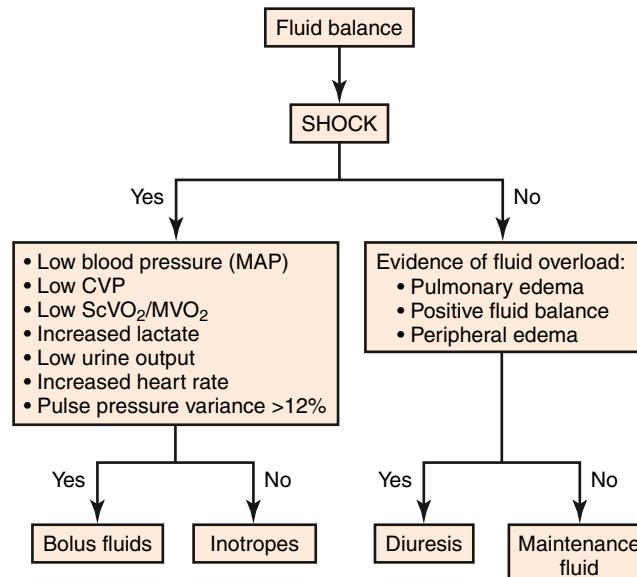
The diagnosis of delirium by CAM requires the presence of BOTH features A and B		
<b>CAM</b> Confusion Assessment Method	<b>A.</b> <b>Acute onset</b>  and <b>Fluctuating course</b>	Is there evidence of an acute change in mental status from patient baseline?  Does the abnormal behavior: <ul style="list-style-type: none"><li>• Come and go?</li><li>• Fluctuate during the day?</li><li>• Increase/decrease in severity?</li></ul>
	<b>B.</b> <b>Inattention</b>	Does the patient: <ul style="list-style-type: none"><li>• Have difficulty focusing attention?</li><li>• Become easily distracted?</li><li>• Have difficulty keeping track of what is said?</li></ul>
<b>AND the presence of EITHER feature C or D</b>		
	<b>C.</b> <b>Disorganized thinking</b>	Is the patient's thinking <ul style="list-style-type: none"><li>• Disorganized?</li><li>• Incoherent?</li></ul> For example does the patient have: <ul style="list-style-type: none"><li>• Rambling speech/irrelevant conversation?</li><li>• Unpredictable switching of subjects?</li><li>• Unclear or illogical flow of ideas?</li></ul>
	<b>D.</b> <b>Altered level of consciousness</b>	Overall, what is the patient's level of consciousness? <ul style="list-style-type: none"><li>• Alert (normal)</li><li>• Vigilant (hyper-alert)</li><li>• Lethargic (drowsy but easily roused)</li><li>• Stuporous (difficult to rouse)</li><li>• Comatose (unrousable)</li></ul>

**Figure 36.4** Confusion Assessment Method (CAM). (From Inouye S, et al. Clarifying confusion: the Confusion Assessment Method. A new method for detection of delirium. *Ann Intern Med*. 1990; 113:941–948.)

delirium (Fig. 36.4). It can be rapidly performed in one to two minutes by nursing staff and is very reproducible. A positive CAM result should alert the clinician to assess variables that could be contributing to DS, such as pre-existing cognitive impairment, advanced age, use of psychoactive drugs, mechanical ventilation, untreated pain, and sleep deprivation.<sup>114,115</sup>

Treatment of delirium can be divided between the use of nonpharmacologic and pharmacologic agents. Nonpharmacologic methods concentrate on early mobilization, sleep protocols, removal of unnecessary noise and stimuli, providing eyeglasses and hearing aids, and frequent re-orientation strategies, particularly with family members. Constant prescribed medication review should be performed to confirm the patient is on the absolutely lowest necessary dose of sedatives and analgesics to prevent pain but avoid disorientation. Pharmacologic agents such as haloperidol have some retrospective data to support their use in the ICU setting for DS. Other antipsychotic and neuroleptic agents – such as risperidone, quetiapine, and olanzapine – are often used in both hyperactive, hypoactive, and mixed delirium. However, these patients must be closely monitored for adverse cardiac and extrapyramidal events associated with these medications.<sup>116–119</sup>

### CHAPTER ALGORITHM



Therapeutic Algorithm: Postoperative Fluid Management. CVP, central venous pressure; MAP, mean arterial pressure; MVO<sub>2</sub>, mixed venous oxygen saturation; ScvO<sub>2</sub>, central venous oxygen saturation.

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# Hospital Readmissions in Vascular Surgery

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## INTRODUCTION

Healthcare spending in the United States has increased dramatically over the past several decades.<sup>1–3</sup> As of 2020, the US spends approximately \$3.6 trillion annually on healthcare, or over 17% of the nation's gross domestic product (GDP) (Fig. 37.1). This is projected to reach over \$6 trillion (almost 20% of GDP) annually by 2028.<sup>1</sup> This unsustainable spending has driven a keen interest in cost containment and the concept of increasing value in healthcare.<sup>4</sup>

While value in healthcare is somewhat easy to define as healthcare outcomes per dollar spent,<sup>5</sup> actually measuring both dollars spent and healthcare outcomes can be quite challenging. Given this, proxies are often used in an attempt to capture outcomes or indicators of quality of care. One such measure that has received a great deal of attention is unplanned readmissions.

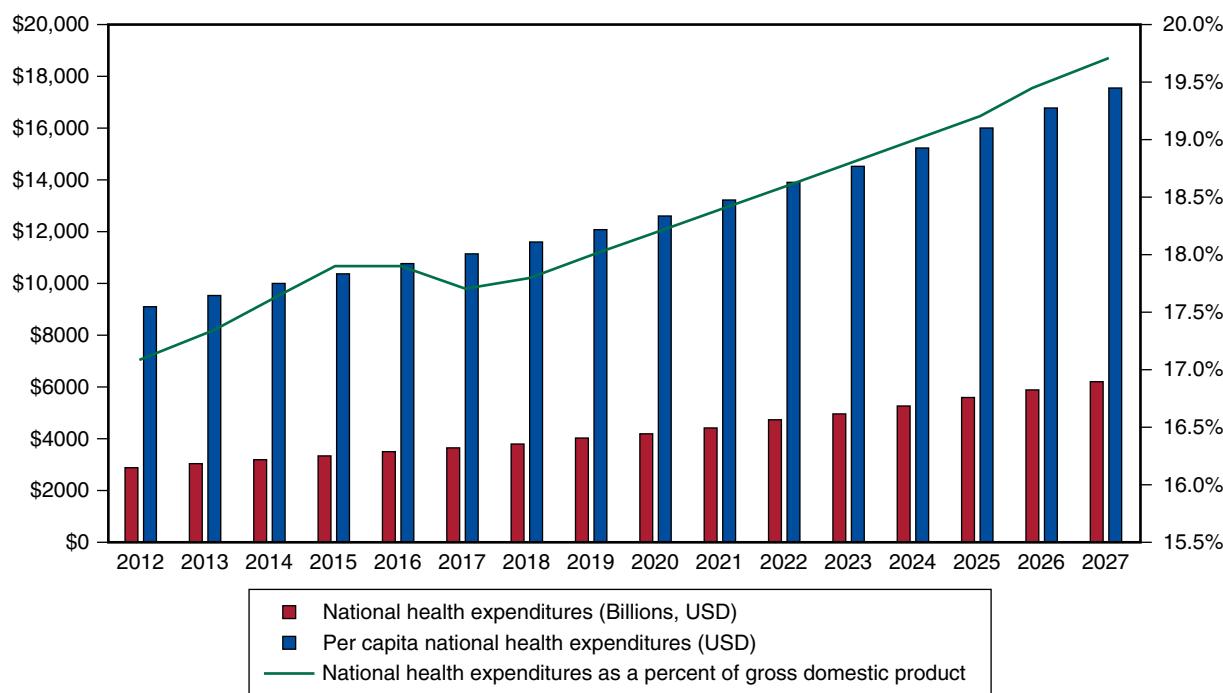
Readmission is a common occurrence that results in increased costs to both patients and to the healthcare system as a whole. It has been estimated that potentially preventable readmissions cost Medicare approximately \$12 billion annually.<sup>6</sup> Under the assumption that at least a fraction of these readmissions are related to breakdown in care and poor transition from the inpatient to the outpatient setting, readmissions have become a marker of quality of a hospital and reducing readmissions has become a focus of healthcare reform and the Affordable Care Act (ACA).<sup>7</sup> This focus on readmissions, specifically 30-day readmissions, as well as the financial penalties that are now tagged to this metric, have driven physicians, hospitals, and healthcare organizations to devote substantial time and effort to minimizing readmission. While on its face avoiding expensive hospitalizations would seem to benefit the system as a whole, emphasizing 30-day readmission as a primary quality

metric, and tagging to it what can be steep financial penalties for hospitals, obscures what could be a holistic view to patient care and moves focus from clinical outcomes to what many have deemed a somewhat arbitrary measure.

Particularly for surgeons, how to best quantify and report quality has been a challenge. As stated by Lord Kelvin, the 19th century mathematical physicist who calculated the point of absolute zero on the thermodynamic temperature scale, "...when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind."<sup>8</sup> For surgical specialties that treat patients with significant comorbidities, readmissions may be driven by factors outside of the surgeon's control.

## HOSPITAL READMISSIONS REDUCTION PROGRAM

The Centers for Medicare and Medicaid Services (CMS) uses a diagnosis-related group (DRG) payment scheme for hospital reimbursement. DRGs were introduced by CMS in 1983 as an alternative to the initial payment model for CMS, which had no incentive to control cost.<sup>9</sup> The DRG system has been revised multiple times since then, and in its current incarnation attempts to capture patient illness severity, comorbidities, risk of mortality, interventions, and likely resource use.<sup>10</sup> Payments are calculated by multiplying the fees by the DRG code plus modifiers for hospital factors including teaching institutions, low-volume hospitals, transfers, and outliers. While unlike direct billing, DRGs attempt to control costs by limiting payments to adjusted but set amounts, they continue to incentivize hospitals to operate at or near capacity in order to bill for patients treated. In addition to the many



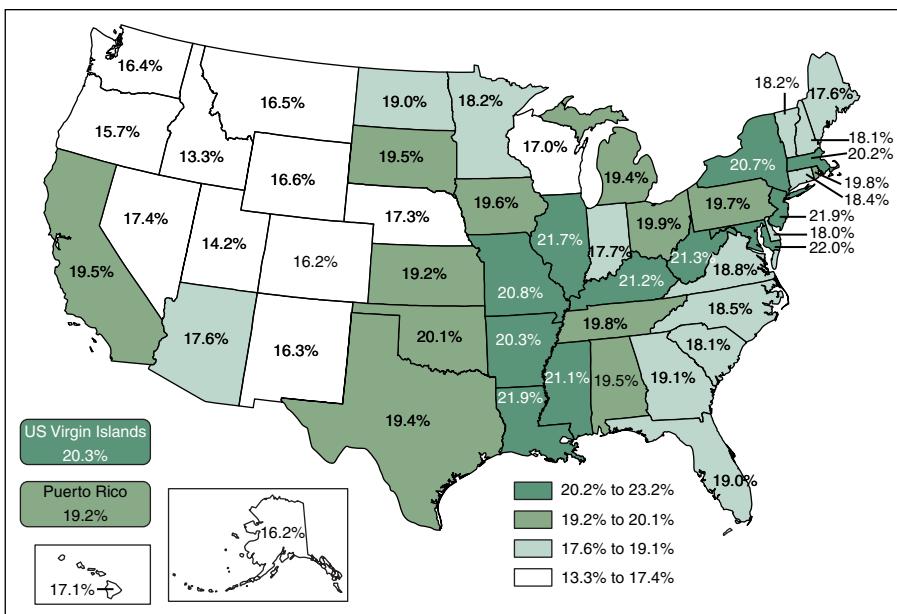
**Figure 37.1** Growth in national health expenditures (NHE) and gross domestic product (GDP), and NEH as a share of GDP, 1989–2015. (From CMS.gov NHE Fact Sheet,<sup>1</sup> <https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/NHE-Fact-Sheet>)

Program year	1	2	3	4	5	6
	Fiscal year	2013	2014	2015	2016	2017
Dates of performance measurement	8-Jun to 11-Jul	9-Jun to 12-Jul	10-Jun to 13-Jul	11-Jun to 14-Jul	12-Jun to 15-Jul	13-Jun to 16-Jul
Conditions for original hospitalization	Heart attack (AMI) Heart failure (HF) Pneumonia	Heart attack (AMI) Heart failure (HF) Pneumonia	Heart attack (AMI) Heart failure (HF) Pneumonia Chronic obstructive pulmonary disease (COPD)	Heart attack (AMI) Heart failure (HF) Pneumonia Chronic obstructive pulmonary disease (COPD)	Heart attack (AMI) Heart failure (HF) Pneumonia [expanded] Chronic obstructive pulmonary disease (COPD)	Heart attack (AMI) Heart failure (HF) Pneumonia [expanded] Chronic obstructive pulmonary disease (COPD)
Maximum penalty	1%	2%	3%	3%	3%	3%

**Figure 37.2** Hospital Readmissions Reduction Program Penalties and Conditions. (From NEJM.org: <https://catalyst.nejm.org/doi/full/10.1056/CAT.18.0194>.)

changes that came with the ACA, a focus of cost control was also implemented and one aspect of that was a focus on 30-day readmissions under the Hospital Readmissions Reduction Program (HRRP).<sup>11</sup> To capture this, CMS calculated anticipated readmission rates based on performance over the prior 3 years and then instituted penalties for institutions that were above that calculated

benchmark. The readmission period is defined as 30 days from discharge rather than from procedure date, an important nuance particularly in surgical specialties, and captures readmission to any part of the hospital, to either surgical or nonsurgical specialties. In 2012, readmission measures began with acute myocardial infarction (AMI), heart failure (HF), and pneumonia (Fig. 37.2). Also



**Figure 37.3** Rates of Rehospitalization within 30 days after Hospital Discharge. The rates include all patients in fee-for-service Medicare programs who were discharged between October 1, 2003, and September 30, 2004. The rate for Washington, DC, which does not appear on the map, was 23.2%. (From Jencks S, Williams M, Coleman E. Rehospitalizations among patients in the Medicare fee-for-service program. *N Engl J Med*. 2009;360(14):1418–1428.)

pertinent to surgeons, in 2014 CMS began to adjust for planned readmissions. Beginning in 2015, chronic obstructive pulmonary disease (COPD) became a tracked condition as well as elective total hip arthroplasty (THA) and total knee arthroplasty (TKA). Coronary artery bypass graft (CABG) was included as of 2017. Once expected risk-adjusted readmissions are calculated, the excess readmission ratio (ERR) is calculated and reimbursement for each targeted DRG is then discounted by that ratio to a maximum penalty of 3% of the hospital's annual DRG payments.<sup>11</sup> The total Medicare penalties assessed in 2017 were \$528 million USD with the average penalty less than 1% of Medicare payments for that institution.<sup>12</sup> Only 1.8% of hospitals faced the maximum 3% penalty.<sup>12</sup>

## READMISSIONS IN VASCULAR PATIENTS

Unplanned readmission varies geographically as well as across specialty (Fig. 37.3).<sup>6</sup> The average estimated readmission rate for Medicare patients for all-comers is as high as 18% and readmission rates vary by geographic area and by specialty, with an average 11.1% of surgical patients readmitted within 30 days of discharge.<sup>6</sup> Within surgical specialties, readmission rates also vary. In a recent study within the VA population, 16% of vascular patients were readmitted within 30 days of discharge compared to only 9.6% of orthopedic patients.<sup>13</sup> Indeed, unplanned readmission rates for vascular surgery patients are high, and range from 9.3% to 24%<sup>6</sup> (Table 37.1). Surgery for peripheral vascular disease had the third highest rate of 30-day readmission behind only congestive heart failure and psychosis.<sup>6</sup> Among surgical patients, individuals undergoing

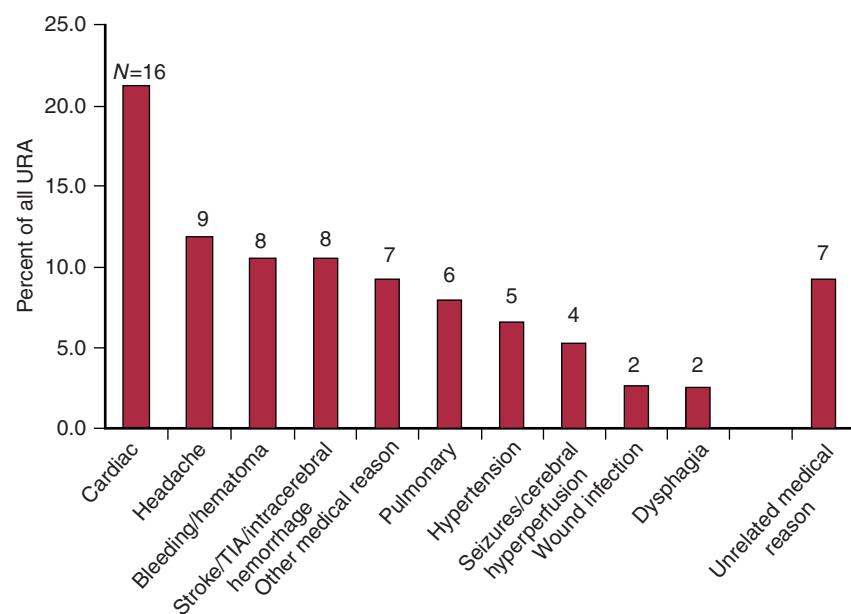
**TABLE 37.1**

Readmission Rates for Vascular Procedures by Procedure Type

Procedure	30-day Unplanned Readmission Rates	Reference(s)
Carotid endarterectomy	6.5%–9.6%	61,62
Endovascular aortic repair	7.6%–13.3%	33,61,63
Open AAA repair	8%–12.8%	33,61
Open aortoiliac bypass	12.3%	64
Endovascular infrainguinal procedures	13.1%–16%	25,64,65
Infrainguinal bypass graft	15.7%–30%	25,61,66–68
AV fistula	26%	16
Type B aortic dissection	14.7%	69
Major limb amputation	28.8%	70

AAA, abdominal aortic aneurysm; AV, arteriovenous

lower extremity bypass have some of the highest readmission rates – 15% at 30 days, compared to only 4% for individuals undergoing hysterectomy.<sup>14</sup> Ninety-day readmission rates climb significantly higher, to an average 17.9% for vascular patients tracked in the ACS NSQIP.<sup>15</sup> This can be as high as 48% following outpatient upper extremity hemodialysis access creation.<sup>16</sup> Following admission for aortic dissection, penetrating ulcer, or intramural hematoma, readmission rates can be as high as 60% with long-term follow-up.<sup>17</sup> Readmissions were often associated with surgical site infections, treated deep vein thrombosis (DVT), and cerebrovascular or cardiovascular events and increased direct hospital costs 61% over the index hospitalization.<sup>15</sup>



**Figure 37.4** Reason for 30-Day Readmission Following Carotid Endarterectomy. Frequency of reasons for unplanned readmission (URA) after carotid endarterectomy (CEA). TIA, transient ischemic attack. (From Ho KJ, Mardini AL, Semel ME, et al. Predictors and consequences of unplanned hospital readmission within 30 days of carotid endarterectomy. *J Vasc Surg*. 2014;60(1):77–84.)

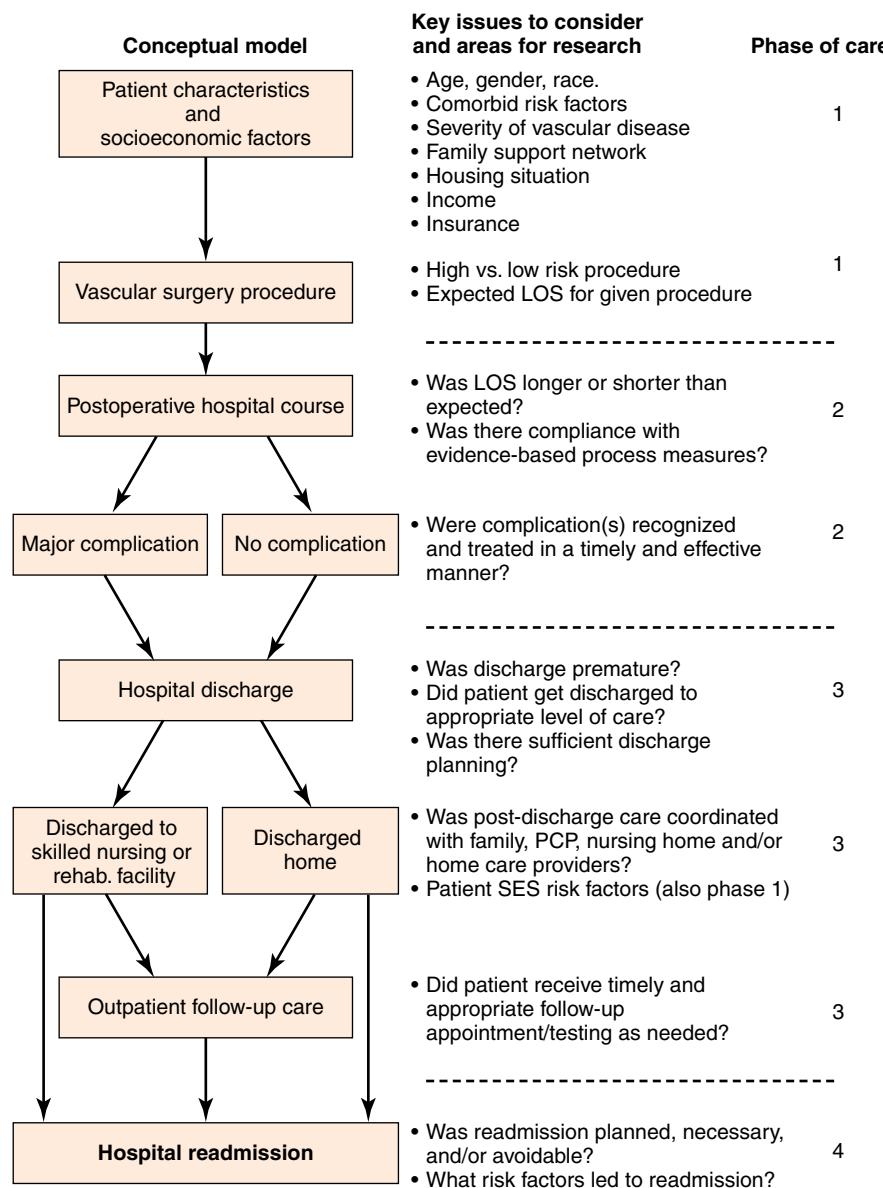
A number of factors have been identified that increase 30-day unplanned readmissions in the vascular population. Estimates of 30-day unplanned readmission following carotid endarterectomy was approximately 6.5%, with cardiac issues being the most frequent reason for readmission (followed by headache, bleeding complications, and stroke). Medical complications other than cardiac, both possibly related to the surgery and unrelated, were also among the most frequent reasons for unplanned readmission following CEA (Fig. 37.4).<sup>18</sup>

Capturing this information is further complicated by the fact that patients are often readmitted to hospitals that did not perform their index procedure. As an example, among patients undergoing emergency general surgery (EGS), approximately 15% are readmitted to a hospital other than that of their index operation. Within the EGS population, readmission to a different hospital and the associated fragmentation of care is associated with an increased risk of mortality; though when adjusted for hospital complexity and severity of patient illness, this difference was no longer seen.<sup>19</sup> Following elective major surgery, including CABG, open abdominal aortic aneurysm (AAA) repair, lower extremity bypass, and joint replacement, readmission to the index hospital was associated with a 26% reduction in 90-day mortality.<sup>20</sup>

Much like patients undergoing emergency general surgery, readmission at a hospital other than that of the index procedure is associated with increased mortality. Among these patients, the most frequent indications for readmission include infection, heart failure, and progressive vascular disease.<sup>21</sup> Among individuals with PAD, over 25% of readmissions for patients undergoing lower extremity vascular procedures have been found to be at a non-index hospital, with female sex, prolonged initial length of stay, and higher Charlson Comorbidity Index

Score being risk factors.<sup>21</sup> Using a statewide database, following complex thoracic and thoracoabdominal aortic aneurysm repair, 79% of readmitted patients were readmitted to a hospital different from that at which their index procedure occurred.<sup>22</sup> Readmissions at the index hospital were more likely to be related to their aneurysm repair, as opposed to readmission to other hospitals which were more likely to be related to medical morbidities.<sup>22</sup> Costs associated with readmissions were lower at non-index hospitals. However, this was possibly related to the increased likelihood of these readmissions being for medical complications. Indeed, in a single institution study, Orr et al.<sup>23</sup> found that readmissions potentially requiring repeat intervention, including endoleaks and graft occlusion, were associated with significantly higher median costs than complications that could potentially be managed nonoperatively including surgical site infections, which, while more common, had a median cost of only \$4,500 rather than \$23,000 for endoleaks and \$17,700 for graft occlusion. While early work suggested no difference has been seen between readmissions for open compared to endovascular procedures on average, recent results from NSQIP found that for individuals undergoing lower extremity revascularization, open lower extremity bypass was an independent risk factor for both all-cause unplanned readmission and procedure-specific unplanned readmission, despite the fact that individuals receiving endovascular interventions were more likely to be of higher physiologic risk.<sup>24,25</sup>

Primary preoperative predictors of readmission include American Society of Anesthesiologists (ASA) operative class, preoperative open wound, inpatient operation, dialysis dependence, and a history of diabetes mellitus. However, as with many surgical patients, the strongest predictors of readmission remain postoperative factors, meaning that they cannot be used



**Figure 37.5** Conceptual Model of Readmission in Vascular Surgery. There are multiple risk factors and key issues to consider at four separate phases of care for a patient readmitted following a vascular surgery procedure. These represent points where variability in clinical pathways and decision making may be associated with increased risk for readmission and where future research may be targeted. LOS, length of stay; PCP, primary care provider; SES, socioeconomic status. (From Brooke BS, De Martino RR, Girotti M, et al. Developing strategies for predicting and preventing readmissions in vascular surgery. *J Vasc Surg*. 2012;56(2):556–562.)

to improve patient selection prior to the operating room.<sup>13,26,27</sup> Among vascular patients, postoperative complications are the most significant predictor of readmission and the complications with this best predictive ability were post-discharge deep space infection, superficial surgical site infections, pneumonia, MI and sepsis.<sup>26</sup> Given that these complications often require hospitalization for management, it is not surprising that they predicted readmission. Among an NSQIP cohort of vascular patients, 40% of unplanned readmissions were related to infectious complications, making an focus on reducing infectious complications a high priority in reducing unplanned readmissions.<sup>27</sup>

## INTERVENTIONS TO DECREASE READMISSIONS IN VASCULAR SURGERY

Brooke et al.<sup>28</sup> reported a framework to address the issue of readmissions in vascular surgery across various phases of care from patient selection to post-procedure follow-up and pointed out the various opportunities for complications in patient care as well as research at each phase (Fig. 37.5).

Within patient selection, multiple patient level factors exist that have been associated with increased risk of readmission

including diabetes and older age. Preoperative health optimization programs, or prehabilitation, are becoming increasingly popular and focus on increased activity, smoking cessation, weight loss, and sleep training among other factors.<sup>29</sup>

At the provider level, while the decreased rates of death and stroke following carotid endarterectomy is a classic example of the impact of surgeon volume on patient outcomes, the link between surgeon volume and readmission remains tenuous.<sup>30</sup> Among pancreatic surgeons, there does appear to be a link between increasing volume of procedures performed and decreased rates of readmission, ranging from 23% for low volume surgeons to 12% for those with higher operative volumes.<sup>31</sup> Nevertheless, the vast majority of variation in readmission appears to be due to patient-related factors, with surgeon-level factors explaining only approximately 3% of variability. At the hospital level, following surgical procedures, higher volume institutions do appear to have lower rates of readmissions, or 16.8% for lower volume hospitals compared to 12.7% for higher volume hospitals.<sup>7</sup>

Patient discharge is also a transition point that influences rates of readmission. Within the state of Maryland, in a study of hospital discharges across multiple services including surgical subspecialties, discharge summaries that were greater than 3 days delayed in completion were associated with an increased risk of readmission and each additional 3-day delay in discharge summary completion was associated with an increase in the adjusted odds of readmission of 1%.<sup>32</sup>

Postoperative care also has a predictably significant impact on readmission rates. Among individuals undergoing open and endovascular AAA repairs, odds of readmission more than doubled for those individuals with a postoperative wound infection and were also significantly higher if patients required discharge to a skilled nursing facility rather than home.<sup>33</sup> What was perhaps most disconcerting is that readmission was also associated with a significant increase in 1-year mortality rates, going from 4.5% to 23.4%.<sup>33</sup>

While there was initial concern that a move towards enhanced recovery pathways (ERP) and earlier discharge could drive increases in readmission rates, in both cases this has not been seen.<sup>34,35</sup> If anything, it appears that standardizing care likely leads to better coordination and fewer deviations from care pathways and that stronger adherence to pathways are associated with better outcomes and decreased readmissions.<sup>36</sup> Specific to vascular surgery, implementation of an ERP for individuals undergoing lower extremity bypass was associated with shorter length of stay and a \$10,000 reduction in total cost as well as a significant reduction in 30-day readmission (21% vs. 7%).<sup>37</sup>

There are also data that suggest that many of the reductions in unplanned readmission rates were potentially related to hospital level changes in response to the initial announcement of penalties related to specific medical diagnoses.<sup>38</sup> For targeted procedures including CABG and hip and knee replacement, readmissions were declining prior to the implementation of procedure-specific penalties, suggesting an anticipatory effect.<sup>38</sup> Following implementation of procedure-specific penalties, readmission rates rather than declining at a faster rate returned to

baseline, suggesting a limited additional impact and potentially a floor beyond which further reductions in post-procedure unplanned readmissions may not be achievable.<sup>38</sup>

Telemedicine and the medical home have also been proposed as potential interventions that may help to reduce unplanned readmission (see Ch. 204, Telemedicine in Vascular Surgery Practice). For patients with heart failure, a group at particularly high risk for readmission and where medication compliance is critical to outcomes, a randomized trial comparing usual care to telemonitoring found no improvement in outcomes including both readmission and death.<sup>39</sup>

## LIMITATIONS OF 30-DAY READMISSIONS

Focusing on 30-day readmissions appears to have at least in part had a positive impact on readmission rates. While readmission rates decreased across the board between 2012 and 2015, rates for targeted conditions appeared to decline more than nontargeted conditions.<sup>40</sup> Further, this occurred without a corresponding increase in observation admissions, a potential loop-hole to readmission penalties.<sup>40</sup> More recently, a spill-over effect has also been seen with reductions in 30-day readmissions for diagnoses and procedures not targeted by the HRRP, again with no increase in observation admissions.<sup>41</sup>

Despite this improvement, 30-day readmission remains a proxy measure for larger issues and the impact of readmission reduction programs on quality of care is less clear. Looking at six major procedures, including CABG, pulmonary lobectomy, colectomy, hip replacement, endovascular aneurysm repair (EVAR) and open AAA repair, an association was seen between 30-day readmission rates and other commonly accepted measures that are felt to correlate with higher quality of surgical care, including higher surgical volume and lower operative mortality.<sup>7</sup> However, adherence to surgical process measures as measured by the Hospital Quality Alliance (HQA) score was not significantly associated with better outcomes.<sup>7</sup>

Specific to vascular surgery, an additional weakness of readmission as a quality indicator for hospitals is the fact that there is little year-to-year reliability in readmission rank for hospitals. Looking at readmissions following open and endovascular AAA repair and lower extremity bypass within Medicare, for 63% of hospitals, the change in their year-to-year rank moved across quintiles, with the previous 2 years' readmission rank explaining only 32% of the variation.<sup>42</sup> The magnitude of this variation is much larger than one would expect based on quality of the hospital alone and suggest that a substantial degree of year-to-year variability may be random.<sup>42</sup>

Measuring readmissions also has the potential to penalize hospitals when in reality it is often community-level factors that influence readmission.<sup>43</sup> Among safety-net hospitals, 30-day readmission following discharge from a general surgical service only appeared to be linked to the index hospitalization in a minority of cases, with the vast majority of the readmissions being related to patient and disposition issues and only 9.2% of all readmissions being related to the initial injury or

condition.<sup>43</sup> In addition, the most frequent reasons for readmission included new soft tissue infections, either related to IV drug use (16.8%) or *de novo* (13.3%), or to disposition support issues (14.5%).<sup>43</sup> Further, the degree to which readmissions, even those that are related to the index hospitalization or hospital-level factors, are preventable has also been raised as a concern. Some estimates report that less than a third of all readmissions are actually preventable.<sup>44,45</sup>

Safety-net hospitals are also disproportionately burdened by the 30-day readmission penalty given the burden of disease faced by many of the patients for which they care. While safety-net hospitals have been able to respond to readmission penalties by reducing readmission rates, CMS has acknowledged this issue with proposed adjustment to penalties based on the socioeconomic demographics of a hospital's patient mix.<sup>46</sup>

An additional concern regarding readmission as a measure of quality is that often factors leading to patient readmission are tied to perioperative complications. If wound complications are captured during the index hospitalization, leading to quality penalties, then lead to a later readmission, clinicians are potentially being doubly penalized.

This is further complicated by the fact that readmission data vary widely by their source. Of estimates of the extent to which readmissions are preventable, the rate varied from 59% for reports based on administrative data to only 12% for those studies that relied on clinical data.<sup>44,45</sup> In another study, when based on administrative claims, readmission diagnosis varied from clinical diagnosis 30% of the time and miscategorized a significant proportion of planned readmissions as unplanned.<sup>47</sup> This raises significant concerns regarding the achievability and appropriateness of lowering 30-day readmissions as a quality metric. Further, where Medicare defines readmission as 30 days from discharge, NSQIP starts the 30-day clock on the day of surgery. This creates what has been described as an immortal time bias, in that individuals with prolonged postoperative admissions are not at risk for readmission.<sup>48</sup> This leads to a systematic underreporting of 30-day readmissions when compared to Medicare data and this is exacerbated by longer hospitalizations.<sup>48</sup>

Both longer and shorter timeframes for readmission penalties have been suggested, with those arguing for a longer duration of surveillance making the point that 30 days likely fails to capture the entirety of post-discharge complications. Shorter timeframes, often 3 to 7 days, have also been suggested as being more directly linked to factors that hospitals have the potential to control.<sup>45</sup> In hierarchical modeling, the impact of hospital-level quality factors on readmission rate nadirs at 7 days post-discharge.<sup>49</sup> It has also been suggested that clinicians feel more personal responsibility for early readmissions, suggesting they may feel more skin in the game when it comes to improving care transitions.<sup>45,50</sup>

A move to a more specific measure of procedure-related readmission, a so-called surgical quality-related readmission, has been proposed. Rather than capturing all unplanned readmissions, it would focus on readmissions related to wound infections, hematoma, other infectious complications, and device malfunctions and may offer a more nuanced approach to capturing quality.<sup>51</sup>

## Existing Interventions To Reduce 30-Day Post-Procedure Readmissions And Alternative Metrics

While the body of literature surrounding the issue of hospital readmissions has grown exponentially, interventions designed to reduce 30-day readmission, particularly following surgical procedures, are lacking and those that are reported are often quite limited in their generalizability.<sup>52</sup> The vast majority focus on improving transitional care, which does appear to be effective in many situations.<sup>53</sup>

Given the potential shortcomings of 30-day readmissions as a quality metric, many have instead focused on financial incentives, bundled payments, risk sharing and Accountable Care Organizations, and on the concept of value in care<sup>54</sup> (see Ch. 200, Alternative Payment Models in Vascular Surgery). Particularly pertinent to procedural care, bundled, or episode-based, payments create a single payment for the complete episode of care. Rather than penalizing hospitals for unplanned readmissions, it is thought that bundles create a financial incentive to minimize low value care or expensive complications. The Society for Vascular Surgery (SVS) Alternative Payment Model Task Force has proposed taking advantage of a CMS Quality Payment Program option, the Advanced Alternative Payment Model (APM) for patients with peripheral arterial disease. The hope is that these bundled payments would improve quality while reducing variability in care and eliminating unnecessary interventions.<sup>55</sup>

It is important to note that, as with readmission penalties and other novel reimbursement strategies, safety-net hospitals, which carry a larger burden of patients with more advanced disease, face disproportionate financial losses in the bundling environment. Patients managed at safety-net hospitals for diabetic foot wounds have more complex disease and are more likely to require an amputation, meaning that safety-net hospitals would face significantly higher penalties for their care compared to other institutions.<sup>56</sup>

Patient-centered outcomes have also become increasingly prevalent, particularly as patient satisfaction begins to play a greater role in the perception of quality care.<sup>57</sup> Within vascular surgery, while graft patency and amputation-free survival are widely accepted outcomes, patient quality of life, independence, and ambulatory status capture a more nuanced picture of the patient experience and also help to allow patients and providers to speak a similar language with respect to expected outcomes and benefits for procedures.<sup>58</sup>

Multidisciplinary care centered around conditions rather than the current specialty-centric silos that exist within clinical medicine has been proposed as a means of decreasing costs and increasing value to patients and the healthcare system.<sup>4</sup> It has been proposed that this would decrease the duplication of effort that plague the current system. Many areas of vascular surgery lend themselves well to this approach. Within orthopedic surgery, setting a common goal and mobilizing a multidisciplinary team was associated with increased early mobilization

and discharge home, all while decreasing costs.<sup>59</sup> A multidisciplinary approach to care for patients with critical limb ischemia was associated with a twofold increase in amputation-free survival.<sup>60</sup>

## CONCLUSION

The issue of cost containment in healthcare has led to a focus on the issue of unexpected readmissions as a potential area of intervention, likely due in part to it being an easily capturable clinical outcome with significant cost implications. While a great deal of work has been done in this area, 30-day readmissions remain something of a blunt instrument when it comes to capturing quality. It is undeniable that unplanned readmissions are costly and can be the result of complications during the index hospitalization, but the degree to which they are a stable measure of quality, or are within the ability of physicians or institutions to improve, seems less clear. A number of alternatives to readmission penalties have been proposed that each attempt to incentivize improved value in care. As the healthcare landscape continues to evolve, it is likely that readmissions will remain a factor in assessing quality of care; however, as our understanding of this process becomes more nuanced, ideally interventions to improve transitions of care will become more prevalent and quality metrics more refined.

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# Normal Coagulation

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Based on a previous edition chapter by Kenneth G. Mann, Laura M. Haynes, and Kathleen E. Brummel-Ziedins

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## INTRODUCTION

Vascular endothelial cells, blood, and extravascular tissue maintain blood flow fluidity or produce an integrated response to attenuate blood leakage by localized clotting at the site of vascular injury. The processes of blood coagulation and fibrinolysis are the primary defense systems of the vasculature. The opposing forces of fibrin clot formation and dissolution

maintain hemostasis and preserve vascular function and integrity. Procoagulant events that culminate in the generation of thrombin and the formation of a fibrin clot protect the vasculature from perforating injury and excessive blood loss. Fibrinolysis removes the clot and initiates mechanisms involved in tissue repair and regeneration. Therefore, hemostasis refers to multiple discrete processes that center on thrombin generation, fibrin clot formation, and fibrin clot dissolution.

Hemostasis is not a passive state, but instead it is actively maintained by the vascular system. Specific cellular and protein interactions are required to maintain a state of equilibrium. When the system is perturbed, an integrated series of processes are required to initiate procoagulant events and to promote fibrinolysis and tissue repair. Each individual process that contributes to hemostasis must operate properly or the entire system is compromised. A balance among procoagulant, anticoagulant, and fibrinolytic factors is required to prevent uncontrolled bleeding or, conversely, excessive clot formation.<sup>1</sup>

## PROCOAGULANT, ANTICOAGULANT, FIBRINOLYTIC PROTEINS, INHIBITORS, AND RECEPTORS

### History and Nomenclature

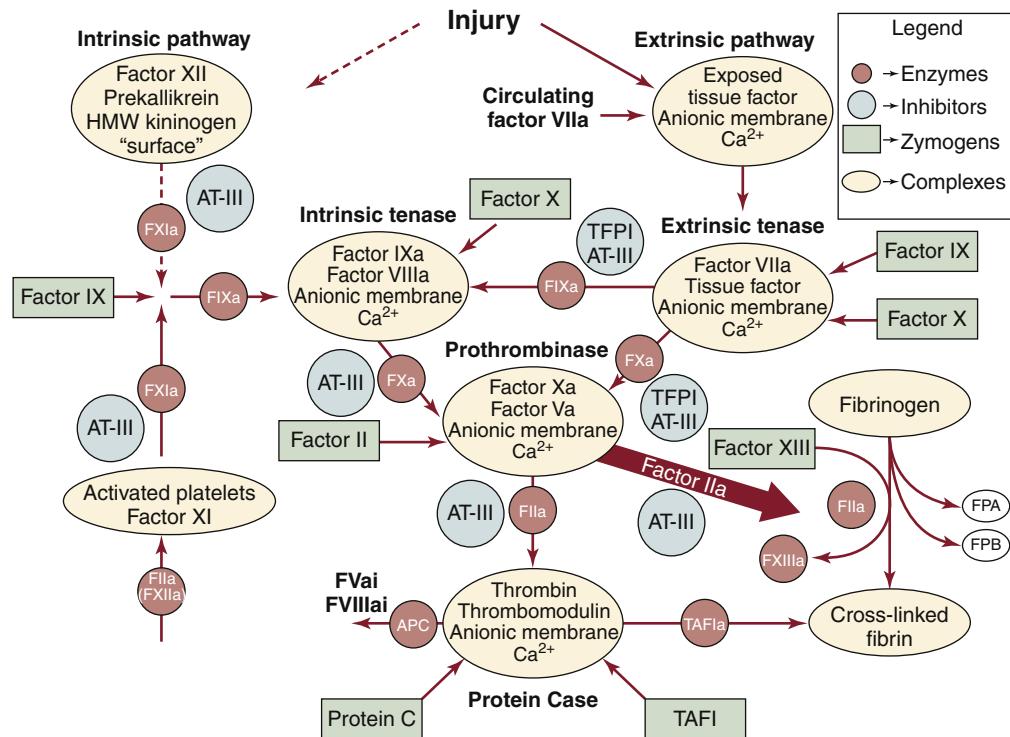
Current knowledge of the components involved in the complex process of blood coagulation (Fig. 38.1) is the result of observations that date back to the 2nd century.<sup>2</sup> Many hypotheses were envisioned about the transformation of fluid blood to a gel-like mass as it escaped the body,<sup>3</sup> but the realization that clots stem blood loss did not occur until the beginning of the 18th century,<sup>3,4</sup> and it was not until the 19th century that the existence of thrombin, the key enzyme in blood coagulation, was recognized.<sup>3,5</sup> Four clotting factors were initially identified<sup>6</sup>: factor I,

fibrinogen; factor II, prothrombin; factor III, thromboplastin; and factor IV, calcium ions (or  $\text{Ca}^{2+}$ ). As more coagulation factors were identified, initially by bleeding pathology and subsequently by laboratory clotting tests,<sup>7,8</sup> they were assigned consecutive Roman numerals, with activated forms distinguished by an *a* after the Roman numeral designation.

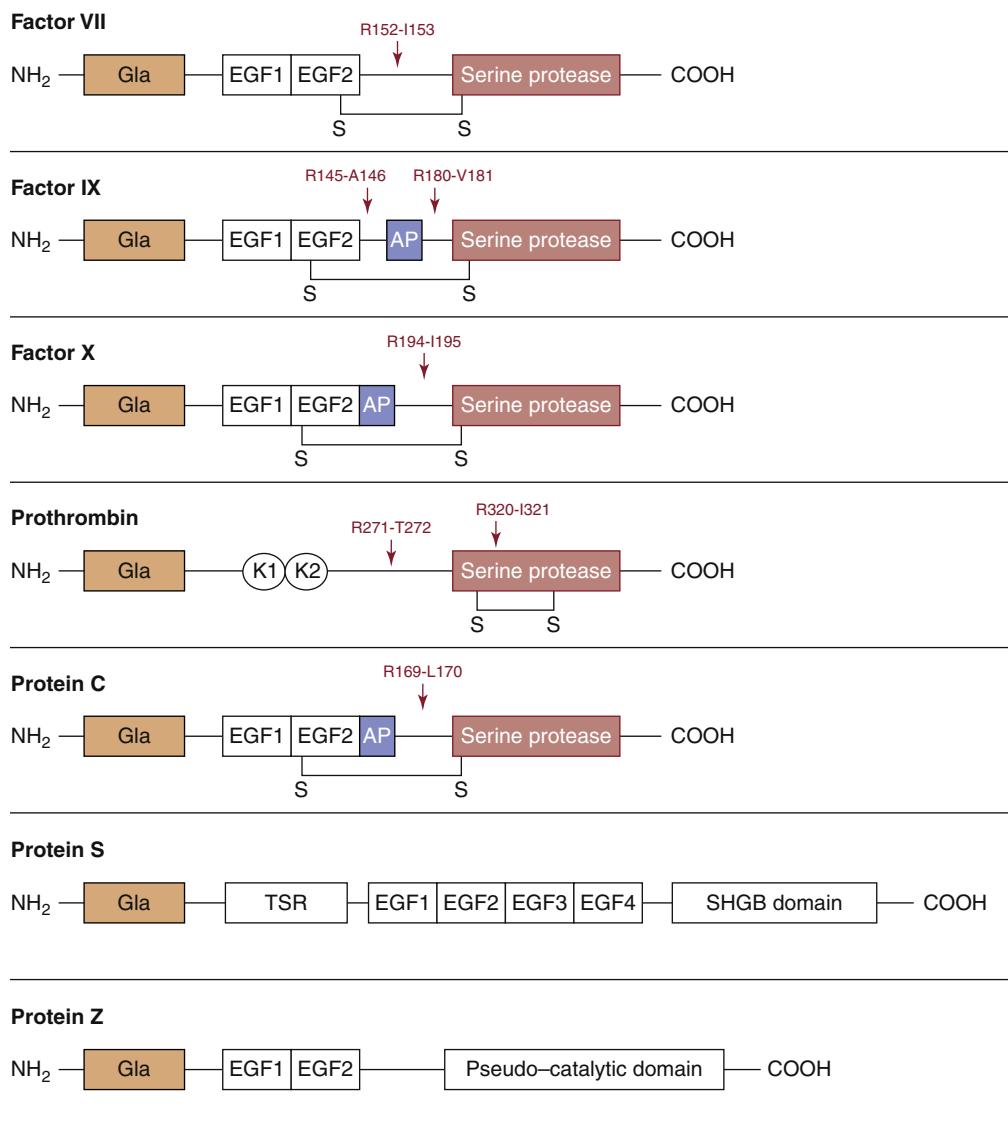
To describe the multiple simultaneous processes involved in generation of a hemostatic response, we identify an inventory of the procoagulant, anticoagulant, and fibrinolytic participants in blood coagulation. Subsequently, we describe the connections between these components and the dynamics of this process.

### Vitamin-K-Dependent Proteins

The vitamin-K-dependent proteins, synthesized in the liver, play central roles in both the procoagulant or anticoagulant pathways. The family includes the procoagulant factors VII, IX, X, and prothrombin and the anticoagulants protein C, protein S, and protein Z (Fig. 38.2 and Tables 38.1 and 38.2). Except for proteins S and Z, these proteins in their active forms are serine proteases. The cleavage of specific peptide bonds converts the vitamin-K-dependent zymogens to their active serine protease forms. All share noncatalytic domains, each of which is characterized by highly conserved regions that provide specific binding characteristics essential for their function. The domain organizations of the vitamin-K-dependent proteins are illustrated in Figure 38.2.<sup>9-13</sup>



**Figure 38.1** Overview of Hemostasis. Two pathways can be used to initiate coagulation: the primary extrinsic pathway (shown on the right) and the intrinsic pathway (shown on the left). *AT*, antithrombin; *HMW*, high-molecular-weight; *TAFI*, thrombin-activatable fibrinolysis inhibitor; *TFPI*, tissue factor pathway inhibitor. (Modified from Brummel-Ziedins K, et al. In: Lee GR, et al., eds. *Wintrobe's Clinical Hematology*. 11th ed. Philadelphia: Lippincott Williams & Wilkins; 2003: Ch. 21.)



**Figure 38.2** Schematic Representation of the Vitamin-K-Dependent Proteins. The building blocks for these proteins include an NH<sub>2</sub>-terminal Gla domain with 9 to 13  $\gamma$ -carboxyglutamate residues followed by either an epidermal growth factor (EGF)-like domain in factor VII, factor IX, factor X, protein C, protein S, and protein Z or kringle (K) domains in prothrombin. Activation cleavage sites, disulfide bonds (-S-S-), and activation peptides (AP) are illustrated. The sex hormone-binding globulin (SHBG) and thrombin-sensitive regions (TSR) are also represented in proteins.

Vitamin K is essential for the biosynthesis of these clotting factors by participating in a cyclic oxidation and reduction process that converts 9 to 13 amino-terminal glutamate residues into  $\gamma$ -carboxyglutamate (Gla) residues.<sup>12,14,15</sup> This posttranslational modification enables the vitamin-K-dependent proteins to interact with Ca<sup>2+</sup> (or calcium ions) and appropriate membranes.<sup>16–18</sup> Inhibition of the Gla residue modification is the basis for “blood-thinning” anticoagulant therapy with coumarin derivatives (e.g., warfarin) that interfere with the redox cycle. The level of anticoagulation achieved with vitamin K antagonist therapy in individuals taking the same dose regimen is variable.<sup>19,20</sup> For instance, altered sensitivity to warfarin has been identified in patients when it is prescribed after surgery.<sup>21</sup> Factors affecting the efficacy of treatment include liver function in the synthesis of clotting factors, the influence of other medications, and the dietary intake/absorption of vitamin

K<sup>22</sup>; therefore, monitoring of warfarin therapy is essential (see Ch. 41, Anticoagulant Therapy).<sup>19,20</sup>

NH<sub>2</sub>-terminal Gla domains are followed by either a Kringle domain or an epidermal growth factor-like domain (see Fig. 38.2). Protein S is not a serine protease precursor but instead contains a thrombin-sensitive region before the epidermal growth factor domain and a sex hormone–binding globulin-like domain in the COOH terminus.<sup>23</sup> Protein Z contains a “pseudo-catalytic domain” in the COOH terminus and is not a zymogen.<sup>24</sup>

### Cofactor Proteins

Cofactor proteins (Fig. 38.3A,B) either circulate in plasma (factor V and factor VIII) or are the cell-bound tissue factor (TF) and thrombomodulin (TM).

**TABLE 38.1** Procoagulant Proteins

Protein	Molecular Weight (kD)	PLASMA CONCENTRATION		Plasma t <sub>1/2</sub> (Days)	Clinical Phenotype Associated with Deficiency	Functional Classification
		(nmol/L)	(μg/mL)			
Factor XII	80	500	40	2–3	None	Protease zymogen
HMW kininogen	120	670	80		None	Cofactor
LMW kininogen	66	1300	90			Cofactor
Prekallikrein	85/88	486	42			Protease zymogen
Factor XI	160	30	4.8	2.5–3.3	Sometimes bleeding	Protease zymogen
Tissue factor	44			N/A		Cell-associated cofactor
Factor VII	50	10	0.5	0.25	Bleeding (occasionally thrombotic)	VKD protease zymogen
Factor X	59	170	10	1.5	Bleeding	VKD protease zymogen
Factor IX	55	90	5	1	Bleeding	VKD protease zymogen
Factor V	330	20	6.6	0.5	Bleeding <sup>a</sup>	Soluble procofactor
Factor VIII	285	1.1–1.5 <sup>d</sup>	0.3–0.4	0.3–0.5	Bleeding	Soluble procofactor
vWF	255	Varies	10		Bleeding	Carrier for factor VIII
Factor II	72	1400	100	2.5	Bleeding <sup>b</sup>	VKD protease zymogen
Fibrinogen	340	7400	2500	3–5	Bleeding <sup>c</sup>	Structural clot protein
Factor XIII	320	94	30	9–10	Bleeding	Transglutaminase zymogen

<sup>a</sup>Factor V Leiden mutation associated with thrombosis.

<sup>b</sup>Prothrombin 20210A mutation associated with thrombosis.

<sup>c</sup>Some fibrinogen mutations associated with thrombosis.

<sup>d</sup>Butenas S, Parhami-Seren B, Mann KG. The influence of von Willebrand factor on factor VIII activity measurements. *J Thromb Haemost*. 2009;7:132–137; Butenas S, Parhami-Seren B, Undas A, Fass DN, Mann KG. The “normal” factor VIII concentration in plasma. *Thromb Res*. 2010;126:119–123.

HMW, high-molecular-weight; LMW, low-molecular-weight; VKD, vitamin-K-dependent; vWF, von Willebrand factor.

**TABLE 38.2** Anticoagulant Proteins, Inhibitors, and Receptors

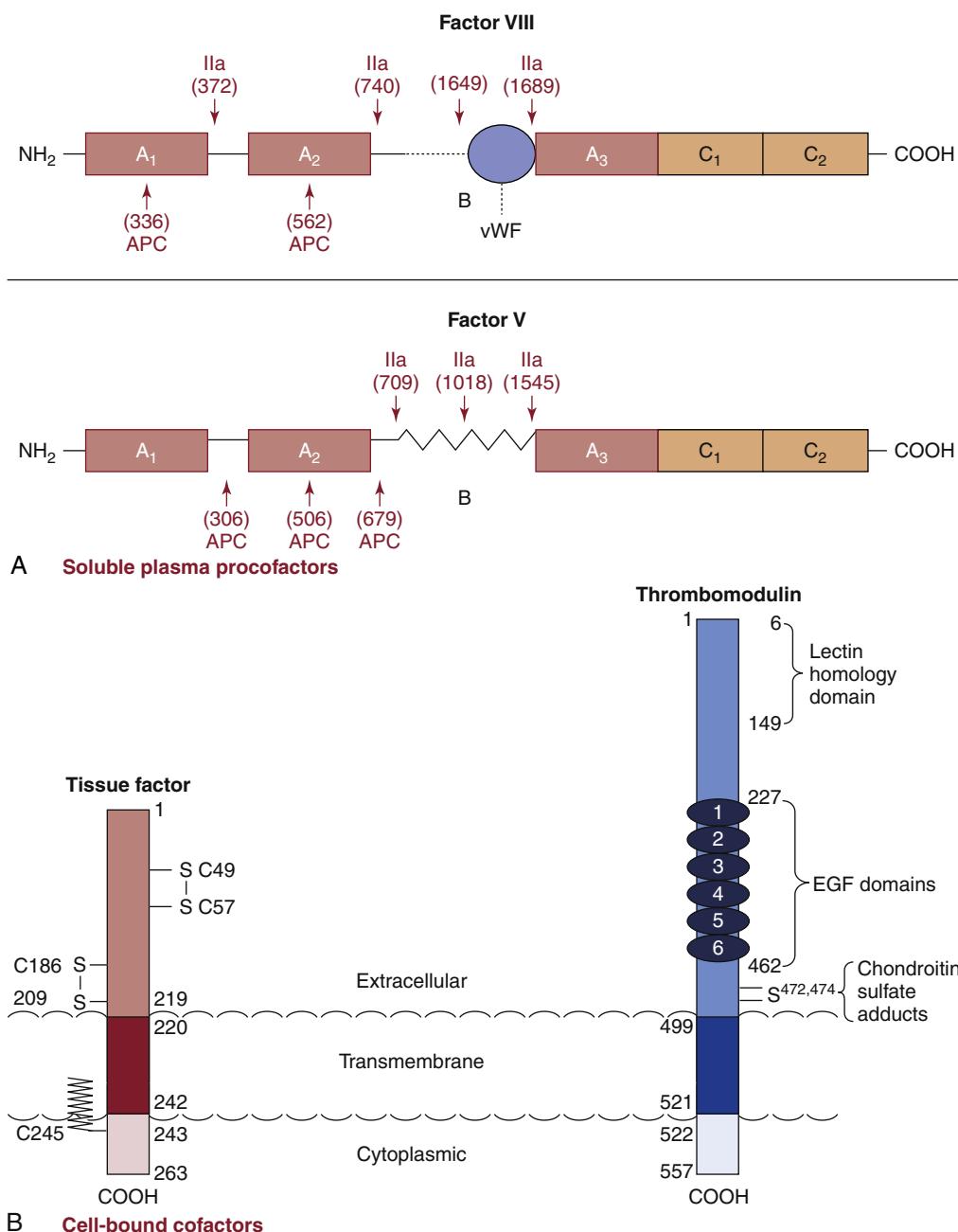
Protein	M <sub>r</sub> (kD)	PLASMA CONCENTRATION		Plasma t <sub>1/2</sub> (Days)	Clinical Phenotype Associated with Deficiency	Functional Classification
		(nmol/L)	(μg/mL)			
Protein C	62	65	4	0.33	Thrombotic	Proteinase zymogen
Protein S	69	300	20	1.75	Thrombotic	Inhibitory cofactor
Protein Z	62	47	2.9	2.5	Sometimes thrombotic	Inhibitory cofactor
Thrombomodulin	100	N/A	N/A	N/A		Cofactor/modulator
Tissue factor pathway inhibitor	40	1–4	0.1	minutes		Proteinase inhibitor
Antithrombin	58	2400	140	2.5–3	Thrombotic	Proteinase inhibitor
Heparin cofactor II	66	500–1400	33–90	2.5	Often thrombotic	Proteinase inhibitor
α <sub>2</sub> -Macroglobulin	735	2700–4000	2–3000	<1h		Proteinase inhibitor
α <sub>1</sub> -Proteinase inhibitor	53	28,000–65,000	1500–3500	6		Proteinase inhibitor
Endothelial protein C receptor						Receptor

### Soluble Plasma Profactors

#### Factor V

Factor V (see Fig. 38.3A and Table 38.1) is a large single-chain glycoprotein<sup>25–28</sup> found in plasma or platelet alpha granules (18%–25% of the total factor V pool)<sup>29</sup> and is secreted upon

platelet activation. It is proteolytically activated by thrombin to form the cofactor factor Va (Fig. 38.3A).<sup>30</sup> Factor Va functions as positive modulator of factor Xa's catalytic potential in the prothrombinase complex in the presence of Ca<sup>2+</sup> and an appropriate membrane surface.<sup>31</sup> It is proteolytically inactivated by activated protein C (APC) (see Fig. 38.3A).<sup>32,33</sup> Cleavage



**Figure 38.3 Cofactors.** (A) Plasma procofactors factor VIII and factor V. The linear domain structures ( $A_1-A_2-A_3-C_1-C_2$ ) are represented. APC, activated protein C; vWF, von Willebrand factor. (B) Cell-bound cofactors tissue factor and thrombomodulin. Epidermal growth factor (EGF), transmembrane, and cytoplasmic domains are illustrated.

at Arg<sup>506</sup> by APC reduces factor Va activity, while the slower cleavage at Arg<sup>306</sup> eliminates activity. The importance of this regulatory mechanism is illustrated by the factor V Leiden, characterized by an Arg<sup>506</sup>Gln mutation.<sup>34</sup> Therefore, despite normal activity in the prothrombinase complex, factor Va Leiden is more slowly inactivated resulting in a prothrombotic phenotype.

### Factor VIII

The procofactor factor VIII circulates in plasma in complex with the large multimeric protein von Willebrand factor (vWF; see Fig. 38.3A). It is homologous (40% identity)

with factor V,<sup>35,36</sup> but circulates in plasma as a two-chain molecule.<sup>37</sup> Factor VIII is activated by thrombin cleavage at three sites to generate the heterotrimeric cofactor factor VIIIa that lacks a vWF binding site.<sup>38</sup> Factor VIIIa enhances the enzymatic activity of the factor IXa in the presence of  $\text{Ca}^{2+}$  and an appropriate membrane surface, forming intrinsic tenase complex. Its function is downregulated by the rapid and spontaneous dissociation of the noncovalently bound  $A_2$  subunit or proteolysis of the factor VIIIa light chain by APC. Deficiency of factor VIII (hemophilia A) is a well-characterized bleeding disorder linked to the X chromosome.<sup>39</sup>

## Cell-Bound Cofactors

### Tissue factor

TF is a transmembrane protein that functions as a nonenzymatic cofactor with factor VIIa in the extrinsic tenase complex that activates both factors IX and X (Fig. 38.4).<sup>40</sup> TF is not expressed in blood in the absence of injury or inflammatory stimulus, and its presentation triggers the extrinsic pathway for hemorrhage control (see Fig. 38.1).<sup>41–43</sup> Functional TF is presented following vascular damage that exposes the subendothelium or cytokine stimulation of monocytes.<sup>44–46</sup> There are no known deficiencies of human TF, and the absence of TF in mice is lethal during embryonic development.<sup>47</sup>

### Thrombomodulin

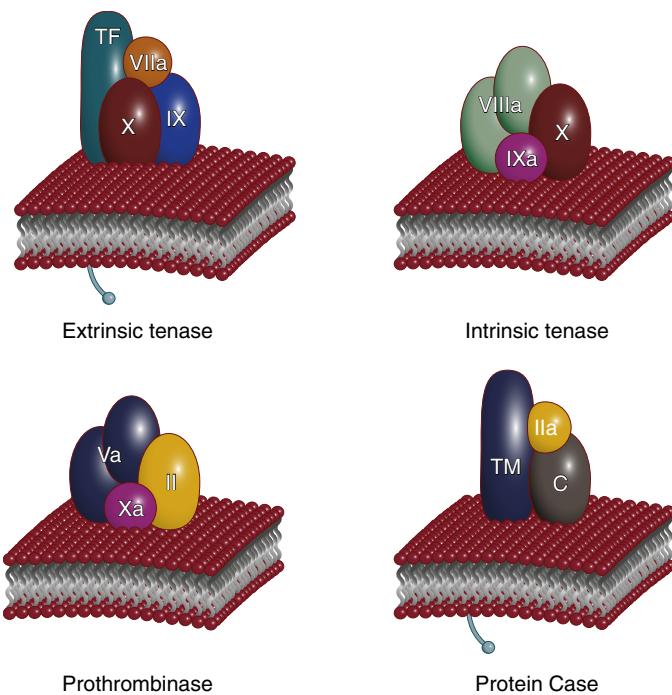
TM is a high-affinity receptor for  $\alpha$ -thrombin and acts as a cofactor for the activation of protein C (see Fig. 38.3B).<sup>48</sup> The endothelial cell protein C receptor provides cell-specific binding sites for both protein C and APC.<sup>49,50</sup> Once thrombin is bound to TM, its procoagulant activities are neutralized and the rate of inactivation of  $\alpha$ -thrombin by antithrombin (AT) is increased.<sup>51–53</sup> Protein C activation by the thrombin-TM complex (protein Case) leads to inactivation of the cofactors factor Va and factor VIIIa, suppressing thrombin formation (see Fig. 38.2).<sup>54</sup> The protein Case complex also has an antifibrinolytic role through activation of thrombin-activatable fibrinolysis inhibitor (TAFI).<sup>55–57</sup> TM activity on the surface of endothelial cells is decreased by inflammatory cytokines<sup>58</sup>; this decrease may contribute to hypercoagulation in inflammatory states.

## Complexes

Vitamin-K-dependent protein complexes are essential for establishing hemostatic balance (Fig. 38.4). Each complex is composed of a serine protease (factor VIIa, factor IXa, factor Xa, or thrombin [factor IIa]), a cofactor that functions as a receptor/enhancer for the enzyme (factor VIIIa, factor Va, TF, TM),  $\text{Ca}^{2+}$ , and an appropriate anionic phospholipid membrane of cellular origin. There are four vitamin-K-dependent enzyme complexes (see Fig. 38.4): the extrinsic tenase complex (factor VIIa-TF), the intrinsic tenase complex (factor IXa-factor VIIIa), the prothrombinase complex (factor Xa-factor Va), and the anticoagulant protein Case complex (thrombin-TM). These membrane-bound complexes serve to localize enzymatic activity to the appropriate regional site for their required enzymatic functions and result in the only biologically relevant enzymatic activity for factor VIIa, factor IXa, and factor Xa –  $10^4$ -fold to  $10^9$ -fold faster reaction rates than the enzyme in solution.<sup>59</sup>

## Intrinsic (Accessory) Pathway Proteins

Deficiencies of proteins associated with the intrinsic pathway (factor XII, prekallikrein, and high-molecular-weight kininogen [HMWK]) are not associated with abnormal bleeding, even after surgical challenge.<sup>60–62</sup> In contrast, deficiencies of the protein components of the extrinsic or primary pathway

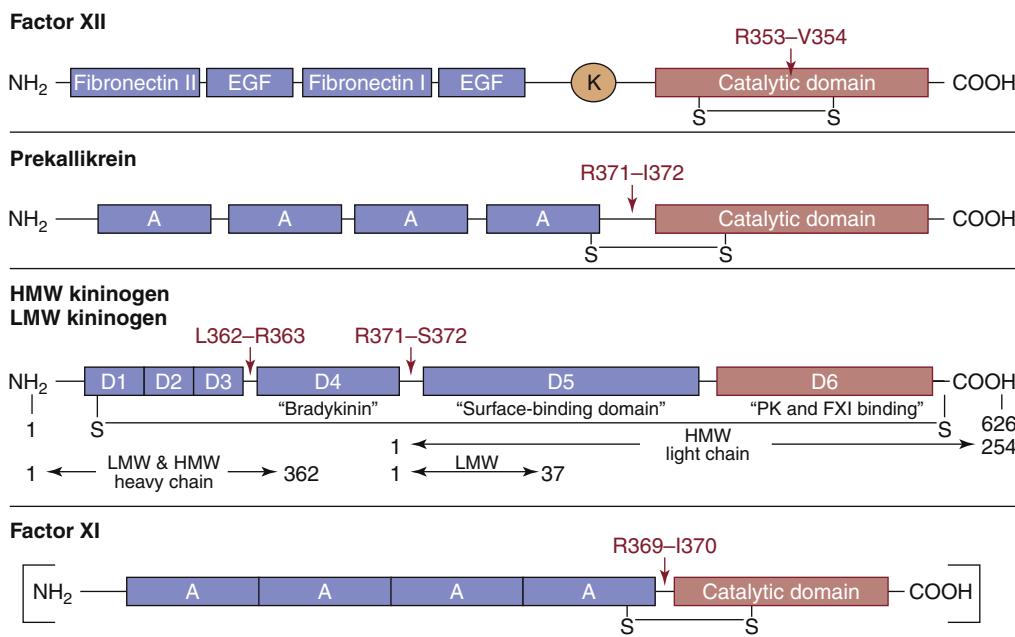


**Figure 38.4** Vitamin-K-Dependent Complexes. Three procoagulant complexes (extrinsic tenase, intrinsic tenase, and prothrombinase) and one anticoagulant complex (protein Case) are illustrated. Each serine protease is shown in association with the appropriate cofactor protein and zymogen substrate or substrates on the membrane surface. Calcium ion is not shown. *TF*, tissue factor; *TM*, thrombomodulin. (Redrawn from Mann KG. *Coagulation explosion*. Vermont Business Graphics; 1997.)

(prothrombin and factors V, VII, VIII, IX, and X) can lead to severe bleeding diatheses.<sup>63–67</sup> The physiologic significance of the intrinsic pathway is still debated, but mounting evidence suggests that it serves as the link between inflammation and innate immunity.<sup>68</sup>

Factor XI represents an intersection point for the two pathways. Individuals with factor XI deficiency (hemophilia C) express variable bleeding with surgical challenge,<sup>69,70</sup> thus establishing a role for factor XI in hemostasis. During the hemostatic process, formation of factor XIa appears to be catalyzed by thrombin as part of a positive feedback loop.<sup>71</sup> Factor XIa then functions in the propagation phase of thrombin generation in association with the primary pathway by activation of factor IX.<sup>72</sup>

Three proteins, factor XII, prekallikrein, and HMWK, are required for activity of the intrinsic pathway. Factor XII and prekallikrein are zymogens that are activated to generate serine proteases, and HMWK is a nonenzymatic procofactor (Fig. 38.5). Activation of this pathway *in vitro* is accomplished when factor XII autoactivates to factor XIIa with exposure to a foreign surface (e.g., glass, kaolin, dextran sulfate, sulfatides).<sup>73–75</sup> The substrates for factor XIIa, prekallikrein and factor XI, exist in a noncovalent complex with HMWK and become activated to kallikrein and factor XIa, respectively.<sup>76</sup> This pathway is positively and negatively regulated via cleavage of HMWK by kallikrein and FXIa, respectively.<sup>77,78</sup> It has also been reported that the intrinsic pathway is activated by inorganic polyphosphates<sup>79,80</sup> or the assembly of these proteins on endothelial cell



**Figure 38.5 Schematic Representation of the Intrinsic Pathway Proteins.** Factor XII, prekallikrein (*PK*), high-molecular-weight (*HMW*) kininogen, low-molecular-weight (*LMW*) kininogen, and factor XI (*FXI*) are shown with their various domains depicted. *A*, apple domain; *EGF*, epidermal growth factor domain; *K*, kringle domain. Cleavage sites and key interchain disulfide bonds (S–S) are shown. For the kininogens, horizontal arrows indicate the amino acid residues defining heavy- and light-chain regions of the activated forms of the cofactors. The factor XI molecule is a dimer of the illustrated monomer. Factor XI is a disulfide-linked homodimer with each subunit containing four apple domains, which provide binding sites for high-molecular-weight kininogen, thrombin, factor XIIa, platelets, and heparin. Activation of factor XI (by thrombin or factor XIIa) results in a conformational change that permits factor IX binding to the apple 3 domain.

membranes.<sup>81,82</sup> Activation of the intrinsic pathway is important in cardiopulmonary bypass because of contact between blood components and synthetic surfaces.<sup>83</sup>

## Stoichiometric Inhibitors

An array of inhibitors is present in blood with both specific and broad-spectrum actions. Inhibitors of clot formation are AT, tissue factor pathway inhibitor (TFPI), heparin cofactor II, and protein C inhibitor (Fig. 38.6).

### Antithrombin

AT is a member of the serpin proteinase family and circulates in blood as a single-chain glycoprotein (see Fig. 38.6).<sup>84,85</sup> Congenital AT deficiency exhibits an autosomal dominant pattern of inheritance, with an incidence of 1 in 2000 to 5000.<sup>86</sup> Individuals with this deficiency have partial expression of AT and are prone to thromboembolic disease (see Ch. 40, Disorders of Coagulation: Hypercoagulable States).<sup>87</sup> The complete absence of AT is lethal. AT is a broad-spectrum anticoagulant, interacting with most proteases participating in the coagulation cascade (see Fig. 38.1), including thrombin, factor Xa, factor IXa, factor VIIa-TF, factor XIIa, plasma kallikrein, and HMWK.<sup>88–90</sup> Heparins and heparan sulfates potentiate these reactions and are used in the treatment of thrombosis. When AT is complexed with heparin, its rate of inhibition of several coagulation proteases is accelerated by up to 10,000-fold as heparin induces structural changes that expose its reactive

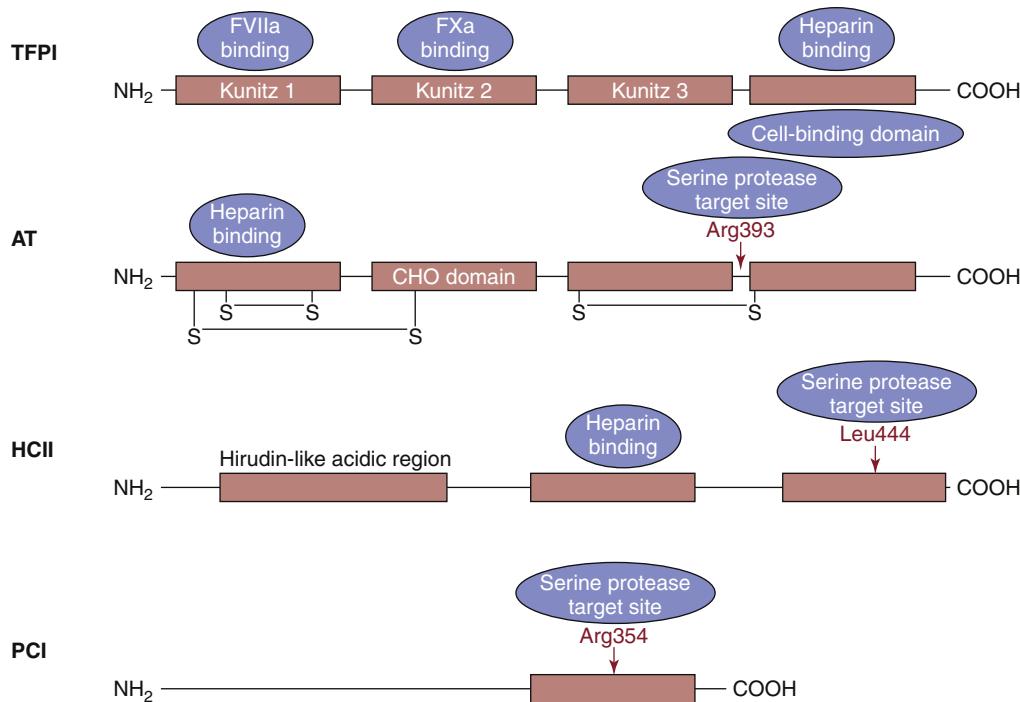
center loop. Antithrombin also displays antiproliferative and anti-inflammatory properties that primarily derive from its ability to inhibit thrombin. In addition, latent or cleaved forms of AT have antiangiogenic activity.<sup>91</sup>

### Tissue Factor Pathway Inhibitor

TFPI (also called “extrinsic pathway inhibitor” or “lipoprotein-associated coagulation inhibitor”) is a multivalent, Kunitz-type inhibitor that circulates in plasma as a heterogeneous collection of partially proteolyzed forms (see Fig. 38.6).<sup>92–95</sup> Ninety percent of circulating TFPI is found associated with lipoproteins.<sup>94,96,97</sup> Circulating TFPI is cleared principally by the liver and has an unusually short half-life compared with other proteinase inhibitors.<sup>98</sup>

Complete deficiency of TFPI is incompatible with birth and survival in transgenic mice;<sup>18</sup> however, this lethality can be rescued by heterozygous or homozygous factor VII deficiency.<sup>99</sup> Mice bred to have a combined heterozygous TFPI deficiency and homozygous apolipoprotein E deficiency exhibit an increased atherosclerotic burden, suggesting a role for TFPI in protection from atherosclerosis and as a regulator of thrombosis.<sup>100</sup>

TFPI is the principal stoichiometric inhibitor of the extrinsic tenase complex (factor VIIa-TF).<sup>101</sup> Effective TFPI inhibition of the factor VIIa-TF complex depends on the presence of factor Xa; thus, inhibition of the extrinsic factor tenase by TFPI occurs only after significant generation of factor Xa. The TFPIα splice variant can also bind to some forms



**Figure 38.6 Stoichiometric Inhibitors.** Tissue factor pathway inhibitor (TFPI) has three Kunitz domains. The Kunitz 1 domain binds factor VIIa, the Kunitz 2 domain binds factor Xa, and the Kunitz 3 domain has been reported to bind protein S. The COOH terminus of TFPI contains a basic region, the cell-binding domain that also binds to heparin and some forms of factor Va. Antithrombin (AT) has two intrachain disulfide bonds (-S-S-) at its NH<sub>2</sub> terminus and one in its COOH terminus with a carbohydrate-rich domain (CHO) in between. The region of interaction between the active sites of target proteases and AT is the reactive center loop, R393-S394. Heparin binding occurs in the NH<sub>2</sub> terminus. Heparin cofactor II (HCII) contains an NH<sub>2</sub>-terminal hirudin-like region, a heparin- or dermatan sulfate-binding region, and a reactive center loop. The reactive site is Leu444.

of factor Va formed early in the coagulation process and inhibit the prothrombinase complex.<sup>102</sup> This interaction is the basis of the east Texas bleeding disorder, which is associated with life-threatening bleeding after trauma or surgery due to the production of a factor V splice variant that binds tightly to TFPIα.<sup>103,104</sup>

### Heparin Cofactor II

Heparin cofactor II is a member of the serpin family (see Fig. 38.6). Like AT, heparin cofactor II inhibits thrombin in a reaction that is accelerated more than 1000-fold by heparin.<sup>105</sup> However, unlike AT, thrombin is the only coagulation enzyme inhibited by heparin cofactor II.<sup>106</sup> Heparin cofactor II and dermatan sulfate levels increase during pregnancy,<sup>107–109</sup> and decreased heparin cofactor II is associated with preeclampsia.<sup>110,111</sup>

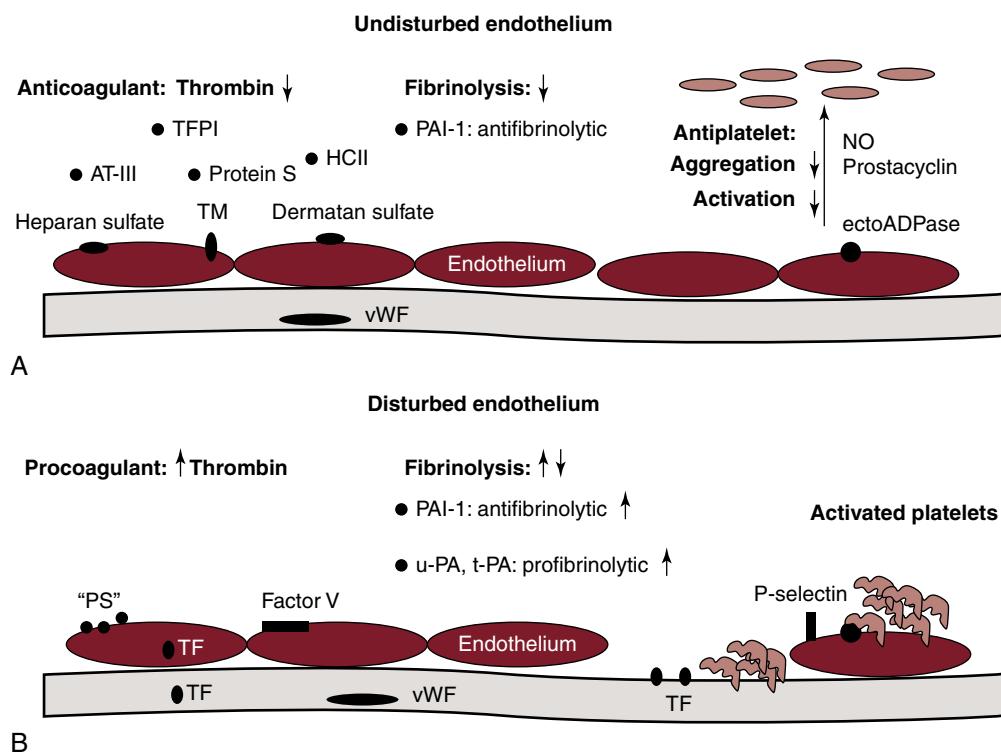
### Endothelium and Platelets

Blood cells and the vasculature are crucial to normal hemostasis, in part because they supply appropriate anionic surfaces to support the coagulation process. Additionally, interactions between the vessel wall, the circulating platelets, and the plasma protein moieties are essential for maintaining blood fluidity (Fig. 38.7A,B). The biologic elements contributing to the phospholipid requirement of the coagulation process include

damaged vascular tissue, activated platelets, and inflammatory cells.<sup>101,112,113</sup> Mechanically damaged cells can provide the anionic membrane required to support general procoagulant complex formation, but more subtle cellular activation events also generate selective complex-forming sites on intact cells, as is the case with platelets.<sup>114,115</sup> Therefore, pathologic hemorrhage is associated with thrombocytopenia, and is also seen in Scott's syndrome, a rare inherited bleeding disorder, in which there is improper presentation of these platelet-binding sites.<sup>116</sup>

### Endothelium

The endothelium plays key roles because of its strategic interface with organs, tissues, and circulating blood, and varies considerably in morphology and physiologic function in different parts of the vasculature. This complex cellular network not only provides a structural barrier to contain flowing blood, but also actively regulates blood pressure, vascular tone, permeability, and processes involving other cells. It also has roles in inflammation, immune responses, and angiogenesis.<sup>117</sup> Therefore, defects in vascular endothelial function have profound physiologic implications. Excessive bleeding can result from structural abnormalities of the endothelial cell layer or supporting matrix. For example, impaired plasminogen activator inhibitor-1 (PAI-1) expression and/or secretion by the endothelium promotes bleeding through increased fibrinolytic activity.<sup>118</sup>



**Figure 38.7** The Endothelium in Hemostasis. (A) Under normal conditions and in the absence of injury or chemical stimulus, the undisturbed endothelium actively downregulates thrombin generation through production of tissue factor pathway inhibitor (TFPI), antithrombin (AT), protein S, heparin cofactor II (HCII), heparan sulfate, thrombomodulin (TM), and dermatan sulfate. The undisturbed endothelium is also antifibrinolytic and secretes plasminogen activator inhibitor-1 (PAI-1). In the absence of stimulus, the endothelium is likewise antiplatelet and prevents platelet adhesion activation, secretion, and aggregation through production of nitric oxide (NO), prostacyclin, and the membrane-associated protein ectoADPase. (B) When the endothelium is disturbed, the endothelium becomes procoagulant and accelerates thrombin formation by exposing or expressing anionic phospholipid ("PS"), limited tissue factor (TF), and factor V. The fibrinolytic response is modulated by the release of both antifibrinolytic and profibrinolytic molecules. Urokinase (urinary plasminogen activator, *u*-PA) and tissue plasminogen activator (*t*-PA) are profibrinolytic and serve to activate plasminogen, whereas PAI-1 inhibits both enzymes and is antifibrinolytic. Platelet activation, secretion, and aggregation are also promoted under conditions in which the endothelium is disrupted. Exposure of von Willebrand factor (*vWF*) in the subendothelial matrix allows platelets to attach to the surface of the vessel. P-selectin likewise promotes platelet attachment.

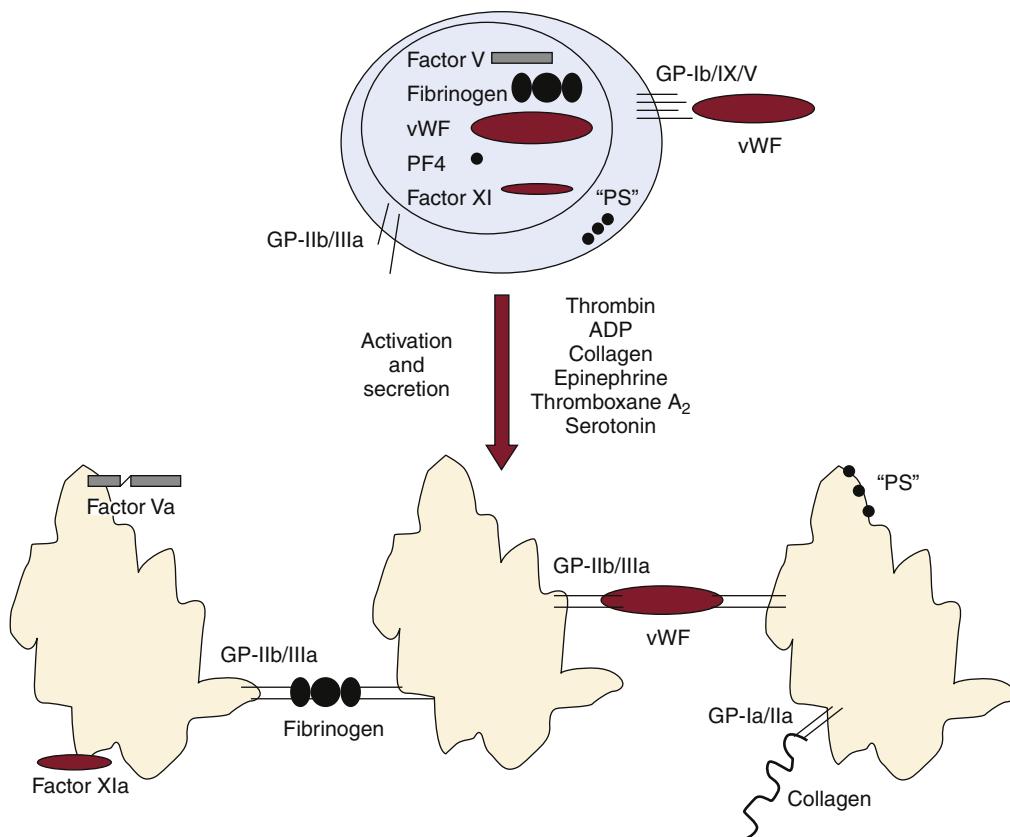
## Platelets

Platelets are vital to procoagulant events and contribute to the fibrinolytic process as well. Like the endothelium, the undisturbed platelet presents a non-thrombogenic surface. Important components of platelet physiology are surface adhesion protein complexes and platelet secretory granules: alpha granules, lysosomes, and dense granules. The contents of alpha granules include procoagulant, adhesive, fibrinolytic, and antifibrinolytic proteins, among others.<sup>29,119–127</sup> In the unstimulated platelet, the granule contents remain internalized, and anionic phospholipids are sequestered in the inner leaflet of the plasma membrane.

When the vascular system is perturbed, platelet plug formation occurs in stages. Initially, platelets adhere and are activated by exposure to collagen, vWF, and other matrix components (Fig. 38.8). However, thrombin is the most potent activator of platelets; it is able to overcome most pharmacologic and cytokine inhibitors that depress platelet function.<sup>128</sup> During platelet activation, the cytoskeleton spreads, platelet-fibrinogen

aggregates are formed, and the contents of the granules are secreted.<sup>129–131</sup> The activated platelets adhere to each other, and to endothelial cells, leukocytes, and components of the subendothelial matrix.<sup>132</sup> The phosphatidylserine-rich internal face of cell membranes is exposed and presents a highly procoagulant surface to the circulation. In addition, activated platelets express specific receptors and/or binding sites for assembly of both the prothrombinase and intrinsic tenase complexes.<sup>114,133–137</sup>

During the extension phase of platelet plug formation, activated platelets accumulate on top of the initial monolayer of platelets bound to collagen. The presence of receptors on the platelet surface allows agonists, such as thrombin, adenosine diphosphate, and thromboxane A<sub>2</sub> to further recruit circulating platelets into the growing hemostatic plug. During this phase of clot growth, close contact between platelets stimulates growth and stabilization of the hemostatic plug, in part through contact-dependent signaling mechanisms.<sup>128,138</sup>



**Figure 38.8 Activation, Secretion, and Aggregation of Platelets.** Platelets have multiple functions in hemostasis. They serve as reservoirs of factor V, fibrinogen, von Willebrand factor (*vWF*), platelet factor 4 (*PF4*), and factor XI. Platelets also contribute a significant portion of the anionic phospholipid ("PS") necessary for membrane-dependent complex formation and function. In the unstimulated state, proteins and other molecules are sequestered in the platelet granules. Anionic phospholipid is found only in the inner leaflet of the platelet membrane and is not exposed to flowing blood. The glycoprotein Ib/IX/V (*GP-Ib/IX/V*) complex that recognizes *vWF* is an active receptor, whereas the *GP-IIb/IIIa* receptor that recognizes a variety of molecules, including fibrinogen and *vWF*, is not active. The *GP-Ib/IX/V* receptor probably allows unstimulated platelets to attach to exposed subendothelial *vWF* and promotes procoagulant events before platelet activation. On activation by a variety of agonists, platelets secrete granule contents, activate and bind factor V/Va and factor XI/XIa, and expose anionic phospholipid. The *GP-IIb/IIIa* receptor serves to link platelets to each other and the vessel wall. Collagen receptors, such as *GP-Ia/IIa*, promote both platelet activation and aggregation.

## Clot Proteins

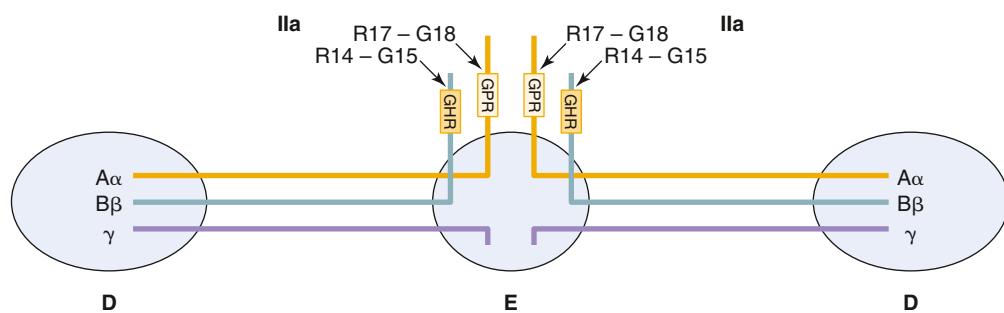
The primary proteins of the clot are fibrin and the transglutaminase factor XIIIa. A central event in blood coagulation is the conversion of soluble fibrinogen to insoluble fibrin (see Fig. 38.1).<sup>139,140</sup> Fibrinogen serves as a molecular bridge to support interplatelet aggregation, and is the precursor of fibrin, the protein scaffolding component of the hemostatic plug (Fig. 38.9). Platelet aggregation critically depends on fibrinogen binding to activated platelets, and depends on fibrin adhesion. Fibrinogen/fibrin also regulates thrombin activity by sequestering thrombin via an exosite mediated interaction.<sup>141,142</sup> Although it is primarily recognized for its role in hemostasis, fibrinogen is also associated with inflammation. Fibrinogen is an acute-phase reactant, with levels increasing during inflammation where it functions as a bridging molecule in cell–cell interactions.<sup>143</sup>

The fibrin clot is stabilized by the transglutaminase factor XIIIa,<sup>144–146</sup> whose function is to cross-link fibrin and other adhesive proteins, including integrin receptors, thereby providing

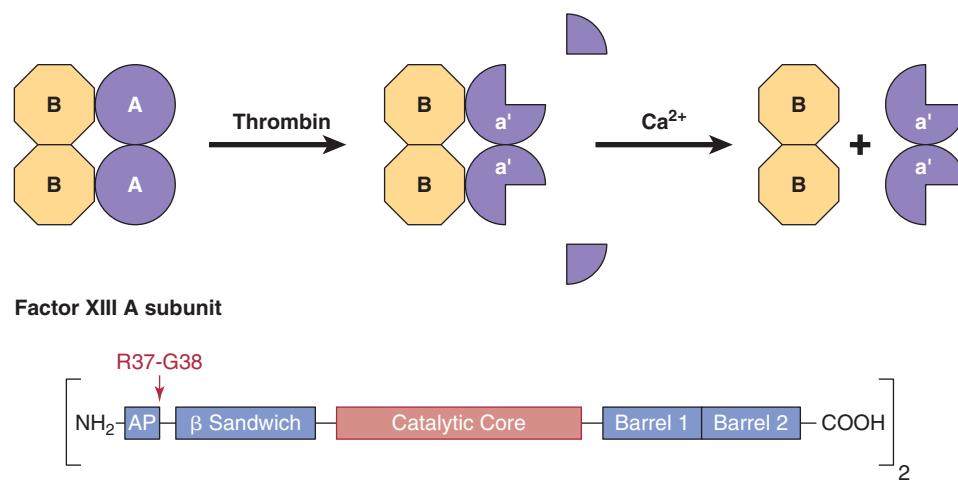
a stable network (Fig. 38.10). The protransglutaminase factor XIII circulates in plasma as a tetramer and is also present as a dimer in platelets. Activation of the protein by thrombin cleavage and  $\text{Ca}^{2+}$  binding yields the transglutaminase factor XIIIa that cross-links fibrin by forming exopeptide bonds between the  $\epsilon$ -amino group of lysine and the  $\gamma$ -carboxamide group of glutamine residues.<sup>147,148</sup> The resulting stable fibrin clot creates an insoluble network that, along with the primary platelet plug, seals the perforation in the blood vessel with a temporary scaffold, stopping further blood loss.

## Fibrinolysis Proteins

Clot formation is integrated with clot dissolution. The mechanisms of clot dissolution center on fibrin-specific reactions. The key proteins involved are plasminogen; the plasminogen activators tissue plasminogen activator (t-PA) and urokinase plasminogen activator (u-PA); thrombin; and the inhibitors PAI-1,  $\alpha_2$ -antiplasmin, and TAFIa (Fig. 38.11 and Table 38.3).



**Figure 38.9** A Schematic Representation of Human Fibrinogen. Fibrinogen is composed of six polypeptide chains (two A $\alpha$ , two B $\beta$ , and two  $\gamma$ ). These are organized into two identical half-molecules. All six NH<sub>2</sub> termini are linked by disulfide bonds in the central or E domain. The three chains extend out from this domain through coiled coils in either direction, terminating in the globular D domains. Thrombin (IIa) cleavage sites at the N termini of the A $\alpha$  and B $\beta$  (arrows) are indicated, with the new N termini (box) that associate with “holes” in the D domains to form fibrin.



**Figure 38.10** Plasma Factor XIII. Thrombin-catalyzed activation of plasma factor XIII (A<sub>2</sub>B<sub>2</sub>; 320,000 Da) occurs in two steps. First, thrombin cleaves the R37-G38 bond. This releases the activation peptides (residues 1–37) from the A chains, producing the inactive intermediate a'2B<sub>2</sub>. In the second Ca<sup>2+</sup>-dependent step, the B chains dissociate from the a'2B<sub>2</sub> intermediate, exposing the active site cysteine, Cys314, of the a' subunits. The enzyme a'2 catalyzes the formation of isopeptide bonds between glutamine residues and lysine residues of adjoining polypeptide chains.

## Fibrinolysis Activators

### Plasminogen/Plasmin

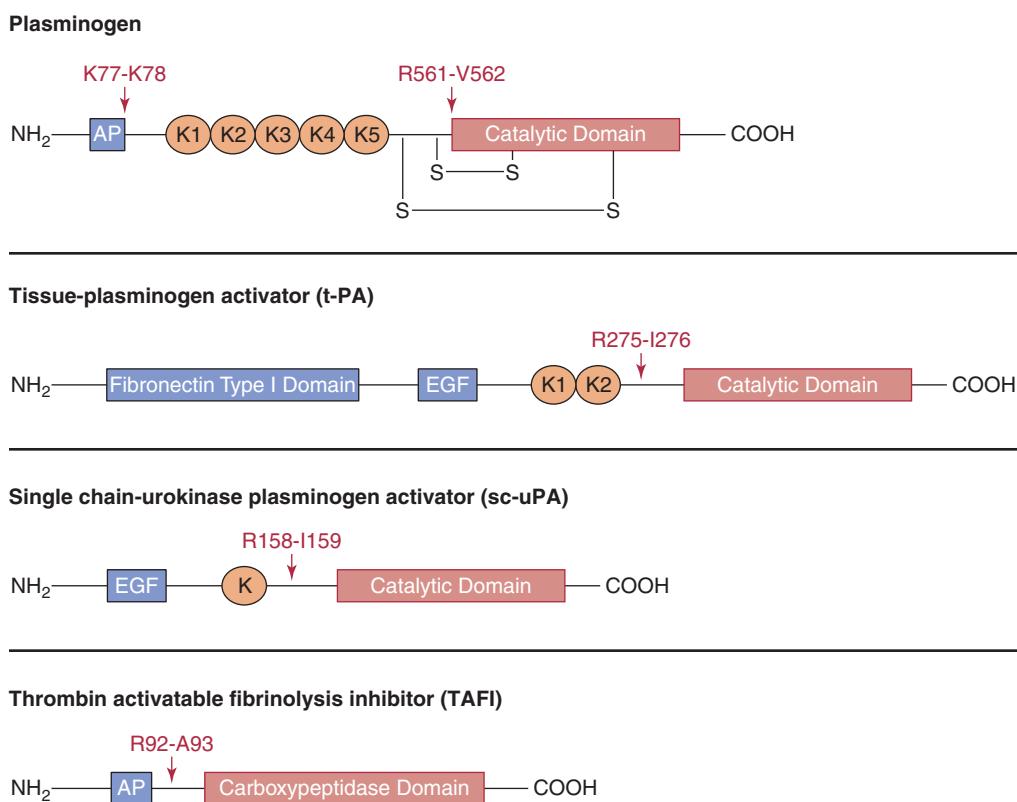
Plasminogen is the inactive precursor of the enzyme plasmin, the primary catalyst of fibrin degradation.<sup>149</sup> Hereditary plasminogen deficiency is described either as a deficiency of plasminogen antigen and activity (type I) or as a normal antigen level but reduced activity (type II, dysplasminogenemia).<sup>150</sup> Plasminogen is also an acute phase reactant protein.<sup>151,152</sup>

Homozygous plasminogen-deficient mice are viable, but exhibit severe thrombosis with systemic fibrin deposition and die prematurely.<sup>153</sup> The zymogen is converted to the serine protease plasmin following cleavage at Arg<sup>561</sup>, primarily by t-PA and u-PA *in vivo* although pharmacologic agents can also exogenously activate plasminogen. Plasminogen activation is primarily inhibited by PAI-1, which targets u-PA and t-PA.<sup>154</sup> Congenital deficiency of PAI-1 is rare, with homozygous individuals displaying abnormal bleeding in response to trauma.<sup>155</sup> Once formed, plasmin cleaves after basic amino acid residues. The lysine analogues  $\epsilon$ -aminocaproic acid and tranexamic acid

can compete with lysyl residues in proteins for binding to plasminogen and hence are inhibitors of fibrinolysis.<sup>156,157</sup> Inhibition of plasmin by  $\alpha_2$ -antiplasmin is the primary route for the regulation of plasmin's hemostatic function *in vivo*; suppression of plasmin activity beyond the locale of fibrin deposition is imperative if systemic fibrinolysis is to be prevented; therefore, plasmin bound through its lysine binding sites to fibrin reacts more slowly with  $\alpha_2$ -antiplasmin than when it is free in solution.

### Tissue plasminogen activator

t-PA manifests its full fibrinolytic potential only when it is bound to fibrin.<sup>158–160</sup> This binding interaction aligns t-PA and plasminogen on the fibrin surface so that the catalytic efficiency of t-PA is enhanced several-hundred-fold. This is vital to the localization of plasmin generation at the site of fibrin deposition. Release of t-PA from the vessel wall is another important regulator of fibrinolysis.<sup>161,162</sup> The rate at which clots lyse depends on how rapidly t-PA is secreted by the relevant cells in the vicinity of an injury.<sup>163,164</sup> For example, activated platelets



**Figure 38.11** A Schematic Representation of Proteins of the Fibrinolytic System. Plasminogen, tissue-type plasminogen activator, urokinase plasminogen activator, and thrombin-activatable fibrinolysis inhibitor are shown with their various domains depicted. Cleavage sites with the specific amino acid residues are shown. *AP*, activation peptide; *K*, kringle domain; *EGF*, epidermal growth factor.

**TABLE 38.3** Fibrinolytic Proteins, Inhibitors, and Receptors

Protein	M <sub>r</sub> (kD)	PLASMA CONCENTRATION		Plasma t <sub>1/2</sub> (Days)	Clinical Phenotype Associated with Deficiency	Functional Classification
		(nmol/L)	(μg/mL)			
Plasminogen	88	2300	210	2.2		Proteinase zymogen
t-PA	70	0.07	0.005	<5 min		Proteinase zymogen
u-PA	54	0.04	0.002	5 min		Proteinase zymogen
TAFI	58	75	4.5	10 min	Thrombotic	Carboxypeptidase
FSAP	64	190	12			Fibrinolytic zymogen
PAI-1	52	0.2	0.01	<10 min	Bleeding	Proteinase inhibitor
PAI-2	47/60	<0.070	<0.005	—		Proteinase inhibitor
α-Antiplasmin	70	500	70	2.6	Bleeding	Proteinase inhibitor
u-PAR	55					Cell membrane receptor

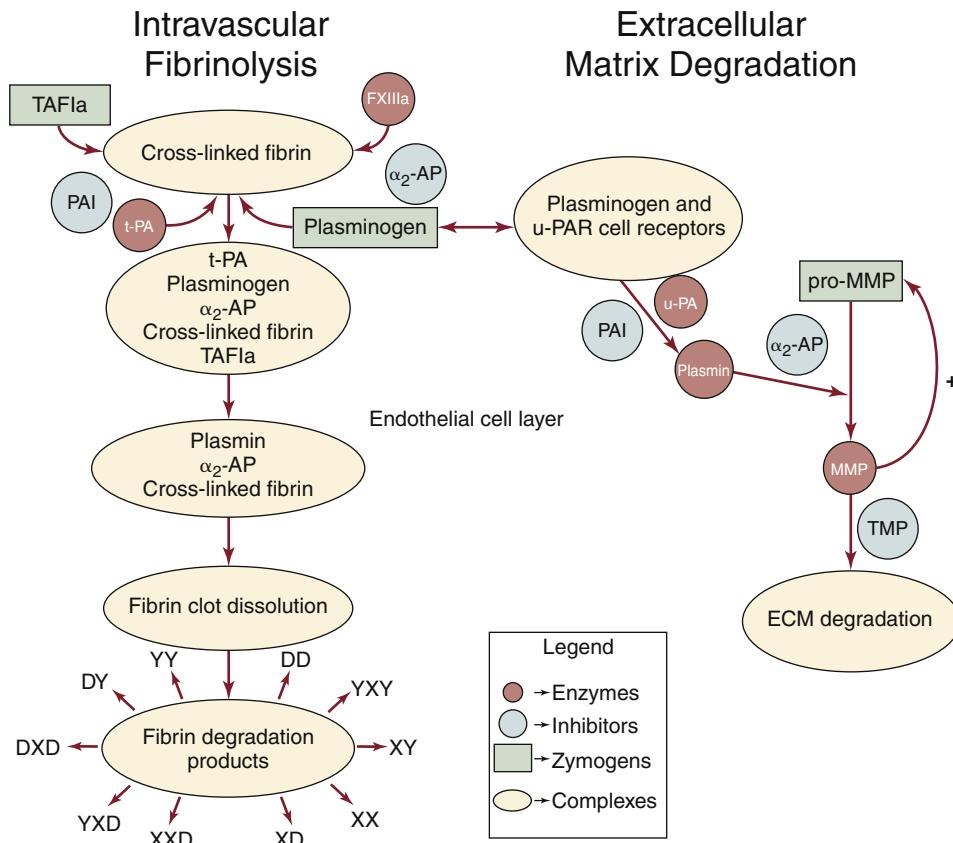
FSAP, Factor VII-activating protease; PAI, plasminogen activator inhibitor; TAFI, thrombin-activatable fibrinolysis inhibitor; t-PA, tissue plasminogen activator; u-PA, urinary plasminogen activator (urokinase); u-PAR, urokinase-type plasminogen activator receptor.

secrete serotonin, which can induce endothelial cells to release t-PA; they also release PAI-1 from their alpha granules. Although only a fraction of this PAI-1 is in the active form, it functions to downregulate plasminogen activation.<sup>165,166</sup> No cases of congenital deficiency of t-PA have been reported (see Ch. 43, Thrombolytic Agents).

#### Urokinase plasminogen activator

The main site of urokinase-driven plasminogen activation appears to be extravascular, where it has an important role in

promoting degradation of the extracellular matrix by triggering the activation of plasminogen and, possibly, matrix metalloproteinases. The regulation of urokinase is important for normal and pathologic processes, including embryogenesis, wound healing, tumor cell invasion, and metastasis.<sup>167–169</sup> Inhibitors of urokinase have been shown to suppress the growth of primary tumors and to interfere with metastasis of tumor cells.<sup>170–177</sup> t-PA appears to be the primary plasminogen activator in the vasculature, with u-PA amplifying rather than initiating plasmin formation.<sup>178,179</sup> Transgenic mice lacking a



**Figure 38.12** Schematic of the Dynamic Interaction Between the Proteins and Inhibitors of Intravascular Fibrinolysis and Extracellular Matrix Degradation. Cross-linked fibrin formation (*left*) is integrated with fibrin clot dissolution and degradation of its products. Two pathways are shown: intravascular fibrinolysis and extracellular matrix degradation, separated by an endothelial cell layer. The enzymes, inhibitors, zymogens, and complexes are illustrated in simplified form to show this multicomponent process. Degradation of fibrin occurs by cleavage of plasmin at the D-E-D domains of fibrin polymers to yield a variety of polymers, as illustrated. Plasminogen can cross the endothelial cell layer and become converted to plasmin by urokinase (urinary plasminogen activator; u-PA) (*right*). Plasmin can convert latent matrix metalloproteinases (pro-MMP) to their active form (MMP). MMPs themselves can act in a positive feedback mechanism to convert pro-MMP to more MMP and ultimately degrade the extracellular matrix. Plasmin-mediated effects are inhibited by plasminogen activator inhibitor (PAI) and α<sub>2</sub>-antiplasmin. MMP-mediated effects are inhibited by tissue inhibitors (TMP). α<sub>2</sub>-AP, α<sub>2</sub>-antitrypsin; ECM, extracellular matrix; *t-PA*, tissue plasminogen activator; TAFI, thrombin-activatable fibrinolysis inhibitor; *u-PAR*, u-PA receptor.

functional *t-PA* gene develop normally and display a normal basal hemostatic phenotype.<sup>180</sup> Mice in which both the *t-PA* and *u-PA* genes are disabled have shortened life spans and experience severe spontaneous thrombotic episodes.<sup>180,181</sup>

### Fibrinolysis Inhibitors

#### Plasminogen activator inhibitor-1

PAI-1, the primary physiologic inhibitor of plasminogen activation in blood, targets *u-PA* and *t-PA* (Fig. 38.12). Congenital deficiency of PAI-1 is rare, with homozygous individuals displaying abnormal bleeding in response to trauma.<sup>182–186</sup> In the normal population, plasma PAI-1 concentrations vary over a 15-fold range (6–80 ng/mL; mean, 10 ng/mL [0.2 nmol/L])<sup>187,188</sup> and exhibit circadian variations.<sup>189</sup> Some of this variability stems from polymorphisms in the PAI-1 gene; however, a larger fraction of the variability appears to derive from the responsiveness of PAI-1 gene expression to a wide

variety of physiologic effectors and conditions as well as pharmacologic agents.<sup>190</sup> Higher levels of plasma PAI-1 delay fibrin removal by shortening the functional lifetime of plasminogen activators, delaying fibrinolysis.<sup>191</sup>

#### α<sub>2</sub>-Antiplasmin

α<sub>2</sub>-Antiplasmin (or α<sub>2</sub>-plasmin inhibitor) is the primary plasmin inhibitor<sup>192–195</sup> and thus is an important regulator of fibrinolysis (see Fig. 38.12). Congenital deficiency of α<sub>2</sub>-antiplasmin is rare, with homozygous individuals displaying a moderate to severe bleeding disorder.<sup>196</sup> The primary site of synthesis is the liver, although the kidney may be another contributing source;<sup>197</sup> its *in vivo* half-life is 2.6 days.<sup>198,199</sup>

#### Thrombin-activatable fibrinolysis inhibitor

TAFI is a plasma procarboxypeptidase B synthesized in the liver and is thought to circulate in blood in complex with plasminogen.<sup>200</sup> Activation of TAFI yields an exopeptidase

(TAFIa) that catalyzes the removal of basic amino acids (arginines, lysines) from the COOH termini of polypeptides. Its primary physiologic activator appears to be the thrombin-TM complex.<sup>201</sup> The COOH-terminal lysyl residues of peptides produced during fibrin degradation are the primary substrates for TAFIa. In the initial phase of plasmin proteolysis of fibrin, peptides are produced that amplify activation of plasminogen by t-PA. These fibrin degradation products contribute to a positive feedback process that accelerates clot lysis. Removal of these terminal lysine residues by TAFIa reduces the number of plasminogen binding sites, thus downregulating the rate of plasmin generation and, thereby, the rate of clot lysis.

## CONNECTIVITY AND DYNAMICS OF BLOOD COAGULATION

In the healthy state, the three-compartment system consisting of vascular endothelium, blood, and extravascular tissue functions to maintain fluidity or to produce an integrated response to attenuate leakage of blood by localized activation at the site of vascular injury. When the endothelium is disrupted, the extravascular compartment and blood interact to rapidly produce a vigorous local coagulation response that attenuates blood loss and initiates the vascular repair process in four phases: initiation, propagation, termination, and elimination/fibrinolysis, which overlap.

### Initiation

Exposure of subendothelial TF activates blood coagulation by binding to circulating plasma factor VIIa.<sup>40,202</sup> Before binding to TF, the plasma serine protease factor VIIa is essentially inert from the catalytic perspective and is, therefore, impervious to the abundant protease inhibitors in plasma.<sup>203</sup> Factor VII competes with factor VIIa for TF binding, thus serving as a negative regulator, buffering the overall reaction. The TF VIIa-factor Xa product complex is under tight supervision by TFPI.<sup>204,205</sup> If the initiating procoagulant stimulus is sufficient to overcome the level of this anticoagulation, a threshold is exceeded and the downstream complexes can form and lead to an explosive burst of thrombin generation. The small amounts of factor Xa produced that escape inhibition by TFPI and AT can activate small amounts of prothrombin to thrombin on an activated membrane surface.<sup>206</sup> Although this process is inefficient, this initial thrombin is essential to the acceleration of the process by serving as the activator for platelets, the procofactors factor V and factor VIII, and factor XI.<sup>72</sup> The initial thrombin also begins activating factor XIII to factor XIIIa<sup>207</sup> while converting some fibrinogen to fibrin,<sup>142</sup> and at this point clot formation is observed.

### Propagation

Once the factor VIIIa is formed, it combines on activated platelets with IXa generated by the factor VIIa-TF complex to form the intrinsic tenase complex. This complex is the major

activator of factor X; it is 50 times more efficient than factor VIIa-TF in catalyzing the activation of factor X<sup>208,209</sup> and is not under the control of TFPI.<sup>210,211</sup> In the absence of factor VIII or factor IX, the intrinsic tenase complex cannot be assembled; therefore, no amplification of factor Xa generation occurs. This is the principal defect observed in hemophilia A and hemophilia B.<sup>212,213</sup>

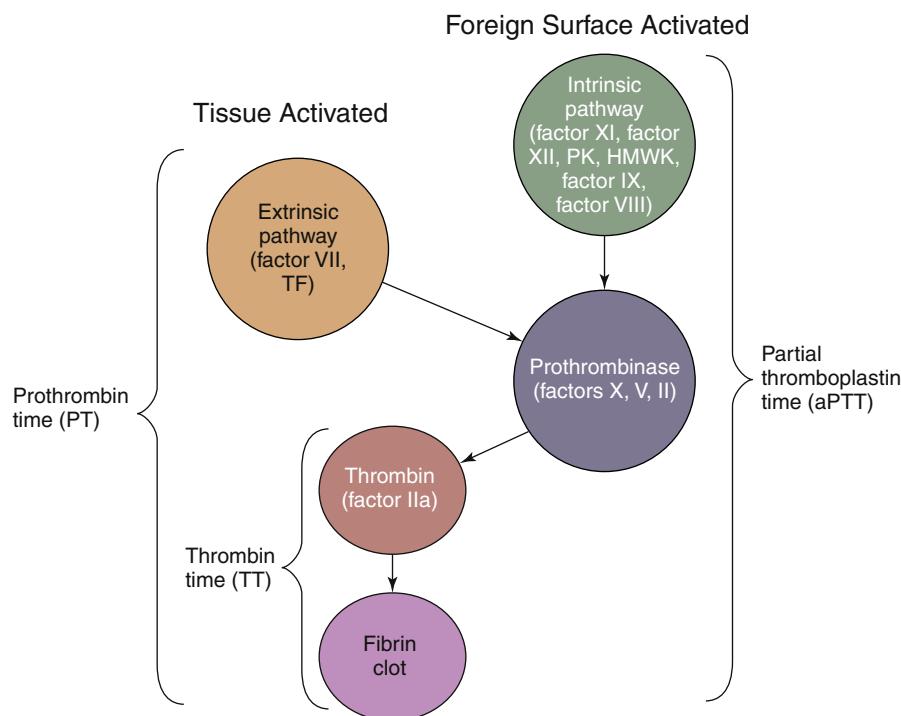
Factor Xa combines with factor Va on the activated platelet membrane and other surfaces at specific receptor sites<sup>114,214,215</sup> to form the prothrombinase complex, the principal generator of thrombin. This process serves as a major amplification loop of blood coagulation. Factors Xa and IXa, of the prothrombinase and intrinsic tenase complexes, respectively, are protected from inhibition by AT and other plasma inhibitors in their complexed form.<sup>216</sup> Furthermore, these membrane-bound enzyme complexes execute the propagation phase of the reaction, during which massive amounts of thrombin are produced efficiently and continuously, as long as more blood enters the wound site to resupply the procoagulant catalytic process.<sup>217,218</sup>

### Termination

Once flow has ceased because of the formation of a fibrin-platelet “dam,” the velocity of thrombin formation diminishes, and the overwhelming concentration of inhibitors present in blood can “catch up” and inhibit the various proteases as they dissociate from their respective complexes. In the intact vasculature surrounding the growing thrombus, procoagulant enzymes and cofactors escaping the wound site are quenched rapidly under normal circumstances by the stoichiometric and dynamic inhibitory systems of blood in cooperation with elements of the vascular endothelium. Any thrombin escaping from the wound site may bind resident TM constitutively present on vascular endothelial cells. When it is TM bound, thrombin is converted from a procoagulant enzyme to an anticoagulant enzyme as part of the protein Case complex. Activation of protein C downregulates the intrinsic tenase and prothrombinase complexes by cleaving factors VIIIa and Va, whereas TAFI activations act to prolong clot lysis.<sup>53,219</sup> When it is operating properly, this system of attenuation of blood leakage displays the appropriate level of procoagulant required to obstruct blood loss, but it is precluded from systemic activation of the coagulation system.

### Elimination/Fibrinolysis

The thrombus restricting blood flow is structurally composed of aggregated platelets and cross-linked fibrin. Other plasma proteins and blood cells are also trapped within the clot. Clot formation is integrated with clot dissolution by plasmin to maintain hemostatic balance. The lytic system has two roles: t-PA generates plasmin at the fibrin surface and governs fibrin homeostasis, whereas u-PA binds to a cellular u-PA receptor and generates pericellular plasmin, which plays an important role in tissue remodeling and cellular migration. The latter function is, to a great extent, mediated by plasmin activation of matrix metalloproteinases, which



**Figure 38.13** Schematic of Plasma Coagulation Tests. The prothrombin time evaluates the tissue factor (*TF*) or extrinsic activated pathway of blood coagulation. This test uses thromboplastin as an initiator of blood coagulation. The plasma test for evaluation of the intrinsic (contact or accessory) pathway is referred to as the partial thromboplastin time. This test uses a foreign surface (e.g., kaolin or silica) as the activator of blood coagulation. The thrombin time, also known as the thrombin clotting time, specifically evaluates conversion of fibrinogen to fibrin through the action of thrombin. *HMWK*, high-molecular-weight kininogen; *PK*, prekallikrein.

degrade the extracellular matrix. t-PA and u-PA are secreted by vascular endothelial cells and regulated by cellular cytokines and components produced during the clotting cascade, including thrombin.

The elimination phase begins the process of tissue repair by dissolving the fibrin-platelet clot generated in the earlier phases of hemostasis. The damaged vascular tissue requires plasmin not only to clear the fibrin clot but also to initiate removal of damaged tissue so that cells can migrate into the injured area.<sup>220,221</sup> Plasmin activates a variety of matrix metalloproteinases that degrade subendothelial matrix components and extricate the damaged tissue.<sup>222,223</sup> These processes mark the beginning of the final stages of the hemostatic response: repair and regeneration.

The importance of tight regulation of these processes is perhaps best illustrated by malfunctions of the hemostatic response. An inappropriate response can lead to one of two opposing but equally undesirable outcomes. Failure to form a sufficient hemostatic plug to arrest blood flow subsequent to vascular injury can result in pathologic hemorrhage. Excessive clot formation or failure to efficiently lyse a clot may result in thrombosis with consequent vascular obstruction. Under normal circumstances, the vascular endothelium together with the aforementioned positive and negative feedback loops within the procoagulant pathways prevents these negative outcomes by actively controlling the coagulation process until a triggering stimulus of sufficient magnitude threatens vascular integrity. Initiation of the procoagulant response also initiates the

fibrinolytic response simultaneously with the repair and regeneration processes.

## BLOOD COAGULATION MONITORING

Most clinical assays use fibrin clot formation as a means to assess hemostasis (e.g., the prothrombin time [PT], activated partial thromboplastin time [aPTT] and thrombin time [TT] assays). These clinical clot-based assays were designed to be rapid; where the formation of a visible clot occurs during the initiation phase of coagulation at only 3% to 5% of the total amount of thrombin produced.<sup>217,224</sup> These clot end point assays have advanced our detection of clinical risk by being able to quickly distinguish certain protein defects in either the intrinsic or extrinsic pathways (Fig. 38.13); however, the majority of thrombin (>95%) is generated after clot formation during the propagation phase,<sup>217</sup> during which most hemostatic and thrombotic physiology is occurring, and is not captured by the fibrin clotting endpoint assays. The development of assays that capture the propagation phase dynamics are leading to a more holistic view of each individual's clinical risk profile.

### Plasma Clotting Tests

Figure 38.13 represents a simplified continuity diagram for the coagulation system and interrogation of that system by

common plasma assays, including the PT, aPTT, and TT. These tests are conducted with citrated plasma.

### Prothrombin Time

The three main uses of the PT assay are the monitoring of warfarin therapy, the assessment of liver function in patients with severe liver disease, and the screening for deficiencies in the extrinsic and common pathways (see Ch. 41, Anticoagulant Therapy). This assay depends on the infusion of  $\text{Ca}^{2+}$  and exogenous TF-lipid preparation (thromboplastin, recombinant, or prepared from human placenta or rabbit brain) to citrated plasma. The intrinsic pathway contributions to coagulation in the PT assay are negligible because of the large amount of TF-lipid used. PT results are standardized by the international normalized ratio (INR).<sup>225</sup> This assay is most sensitive to factor II, factor V, factor VII, factor X, and fibrinogen; however, mild deficiencies in any of these factors can go undetected with the PT assay. A PT test may be called an INR (International Normalized Ratio), which reflects a method of standardizing the results of the PT test irrespective of the testing method.

### Activated Partial Thromboplastin Time

The continuity of the intrinsic pathway of coagulation is assessed by the aPTT, which involves adding phospholipid,  $\text{Ca}^{2+}$ , and a foreign “surface” (e.g., kaolin or silica) to citrated plasma in the absence of TF.<sup>8</sup> This test evaluates the ability of the intrinsic pathway catalysts (i.e., factor XII, prekallikrein, HMWK, factor XI, factor VIII, and factor IX) and components of the common pathway (i.e., fibrinogen, prothrombin, factor V, and factor X) to produce a clot. The primary utility of the aPTT is that it provides identification of the congenital hemostatic defects associated with hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency). The aPTT is also used to monitor therapy with unfractionated heparin and to detect the lupus anticoagulant.

### Thrombin Time

The TT test detects direct inhibitors of thrombin or fibrin polymerization. It is particularly sensitive to heparin, fibrin degradation products, and hypofibrinogenemia or dysfibrinogenemia. Thus, this screening test is useful in evaluating a prolonged PT or aPTT by discriminating between a problem in thrombin generation and the inhibition of thrombin activity.

### Thrombin Generation Assays

Aberrations in thrombin generation can affect the critical balance of many hemostatic processes that ultimately can result in bleeding and/or clotting. An integrated view of the ability of recalcified platelet-rich or platelet-poor plasma samples to generate thrombin on stimulation with either contact pathway activator or TF has more recently come into use. In the thrombin generation assay (TGA), thrombin, once produced, hydrolyzes a specific substrate to give a fluorescent signal that is continuously recorded and to provide an evaluation of the phases of thrombin generation.<sup>226–228</sup>

This assay has recently been adapted for use in whole blood,<sup>228</sup> and continued adaptations of TGA will ultimately

lead to improved correlation between the diagnostic value of these tests and clinical outcome.<sup>229,230</sup>

## Platelet Function Tests

Platelet function tests are used to aid diagnosis (e.g., impaired platelet function or thrombocytopenia), predict risk (e.g., hemorrhage or thrombosis), and monitor antiplatelet therapy (see Ch. 42, Antiplatelet Agents). If platelets are not functioning normally or a thrombocytopenia is present, a patient is at an increased risk of excessive bleeding. A platelet count continues to be utilized as a first-line test, but the overall function of the platelet is more difficult to measure. Platelets are sensitive to manipulation and are prone to spontaneous activation *in vitro*. Assays to test platelet function include platelet aggregometry, platelet function analyzers, flow cytometry, and molecular biology techniques.<sup>231–233</sup>

### Platelet Aggregometry

Platelet aggregometry allows the laboratory to test how particular stimulators (agonists) affect platelets in the milieu of plasma or whole blood. This test is used to diagnose inherited and acquired platelet function disorders. It is affected by aspirin and a variety of other drugs that alter platelet function. Platelet aggregometry does not mimic the physiologic processes of platelet adhesion, activation, and aggregation that occur during hemostasis *in vivo*. Other tests have been developed to simulate the *in vivo* processes that occur during vessel wall damage.

### Instruments that Simulate Platelet Function *In Vitro*

The Plate Function Analyzer-100 (PFA-100) is the mainstay for platelet function screening in hospitals and screens platelet adhesion and aggregation under high shear conditions in response to defined agonists.<sup>234,235</sup> This test is sensitive to both platelet count as well as hematocrit. Although abnormal results are indicative of platelet dysfunction, they are not specific for any disorder. Furthermore, it has not been shown to be able to predict the likelihood that a patient will bleed excessively during surgery, and its full clinical utility is still being established.

Other platelet function tests have been developed to address existing gaps in our ability to analyze platelet function<sup>235</sup>: the Clot Signature Analyzer (CSA) can detect abnormalities in both global hemostasis and platelet function under high shear conditions,<sup>236,237</sup> while the Thrombotic Status Analyzer (TSA) measures both thrombotic and thrombolytic activities within nonanticoagulated blood<sup>238</sup> and is capable of detecting defective or excessive platelet function, and monitoring both antiplatelet and thrombolytic therapy. The VerifyNow system was developed to address the need for monitoring platelet receptor blockade in order to ensure optimal dosing of anti-GPIIb/IIIa therapy.<sup>239</sup> Finally, thromboelastography (described below) also tests platelet function in the context of the coagulation process.

## Whole Blood Assays

There is renewed interest in “global coagulation testing” with methods enabling on-site measurements of coagulation that

provide rapid and continuous information on coagulation. The use of whole blood gives a better picture of the situation *in vivo* because all the blood components are allowed to interact during the test. The whole-blood, on-site assays in common use in surgery and cardiovascular percutaneous interventions are the activated clotting time (ACT) and thromboelastography.

### Activated Clotting Time

The ACT, introduced by Hattersley in 1966,<sup>240</sup> is an adjusted aPTT test for samples of citrated whole blood. The ACT assay can evaluate the influence of coagulation inhibitors, such as heparin and the direct thrombin inhibitors.<sup>241,242</sup> It is one of the most frequently performed coagulation assays and has shown utility as a point-of-care evaluation of the hemostatic response in surgical and interventional suites to control treatment with intravenous unfractionated heparin during vascular procedures.<sup>243</sup>

### Thromboelastography

Thromboelastography uses technology that has existed for more than 40 years.<sup>244,245</sup> The modern iterations of the thromboelastograph are computerized, user-friendly devices that provide on-site evaluations of clotting performance and the potency of *in situ* fibrinolysis. These devices are viscometers that measure the increasing viscosity of blood during the coagulation process, producing a time-based record. Viscoelastic measurements are currently being performed on one of two instruments using their proprietary reagents: rotational thromboelastography (ROTEM) and thromboelastometry (TEG). The thromboelastogram arises through movement of the cup (TEG) or the pin (ROTEM). As fibrin forms, this movement is impeded and transformed to a trace (Fig. 38.14) reflecting different phases of the clotting process from which different semi-quantitative parameters that evaluate the quality and timing of clot formation and lysis are measured, including clot time (R), clot build-up and cross-linking (K and  $\alpha$ ), and overall strength of the fibrin clot (maximum amplitude, MA). Protracted

evaluations yield parameters associated with clot lysis. To describe these viscoelastic changes, both systems have their own terminology. The viscoelastic measurement of a patient's blood sample is increasingly being used in clinical settings.<sup>246</sup> These settings include cardiac surgery,<sup>247–250</sup> liver transplants,<sup>251</sup> sepsis trauma,<sup>252–259</sup> obstetrics,<sup>260</sup> anticoagulant activity,<sup>261,262</sup> and treatment with fibrinolytic agents.<sup>263–267</sup> Modifications of thromboelastography to measure platelet aggregation are also being utilized more in the clinical setting.<sup>268,269</sup>

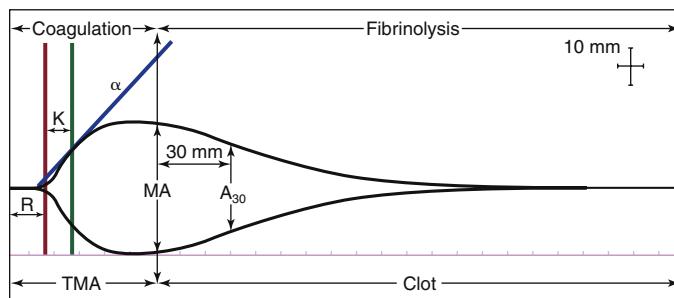
## FUTURE COAGULATION ASSAYS

Advancing technology will permit the translation of our ever-expanding understanding of blood coagulation physiology into even more refined and informative clinical assays. The advent of new, direct-acting procoagulants and anticoagulants is leading to the push for the development of new plasma-based and on-site whole-blood assays that will improve the reporting of the quality of an anticoagulant response, its monitoring, and its reversal.

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



**Figure 38.14** Representation of a Thromboelastographic Tracing. Evaluation of the quality and timing of clot formation and lysis is illustrated in terms of semi-quantitative parameters: *R*, the reaction time, estimates the time to initial clot formation; *K* and  $\alpha$  estimate the rate of fibrin formation and cross-linking; *MA* estimates the maximum amplitude of the fibrin clot and its strength; *TMA* calculates the time to *MA*.  $A_{30}$  is the amplitude at 30 minutes.

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# Disorders of Coagulation: Hemorrhage

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Based on a previous edition chapter by Jeffrey H. Lawson and Elisabeth T. Tracy

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## INTRODUCTION

Understanding the complex biology of coagulopathy and hemorrhage is critical to the perioperative management of surgical patients. “Coagulopathy” is a term employed loosely in the literature and in the clinical setting. Coagulation is a physiologic defense mechanism aimed at maintaining the integrity of the circulatory system in the setting of vascular injury. There is a critical balance between coagulation and fibrinolysis aimed at preventing pathologic hemorrhage and thrombosis. Indicating “abnormal coagulation,” coagulopathy refers to both an excessive bleeding as well as thrombosis<sup>1</sup>; however, is most commonly used to refer to a tendency towards hemorrhage. It is applied both to patients with and without an identifiable coagulation abnormality on laboratory testing, which may be acquired or inherited.

Patients with vascular disease and those undergoing vascular surgery frequently pose complex hemostatic challenges – they are often elderly with cardiovascular comorbidities, may have uremia-related platelet dysfunction, are frequently on anti-platelet or anticoagulant therapy, and commonly require intraoperative anticoagulant therapy. Thus, the vascular surgeon is tasked with preventing adverse events by achieving adequate hemostasis without effecting extensive thrombosis. An understanding of normal and abnormal hemostasis is necessary to assimilate the pathophysiology of the coagulopathies and necessary treatments (see Ch. 38, Normal Coagulation).

## DIAGNOSIS AND PREOPERATIVE SCREENING FOR BLEEDING DISORDERS

Identifying patients at risk for bleeding preoperatively allows the surgical team to initiate corrective treatment before performing a surgical procedure and to plan for optimal perioperative management. Evaluation for a possible bleeding diathesis starts with a screening based on history and physical examination, which help guide the appropriate laboratory evaluation. When the history and physical or initial laboratory evaluation is suggestive of a bleeding disorder, specialized medical or hematologic consultation should be considered for preoperative evaluation and optimization.

## History and Physical Examination

A detailed history should elicit any previous episodes of bleeding with prior surgery, dental extractions, or trauma as well as any hematuria, melena, easy bruising or epistaxis. It is particularly important to inquire about previous hemostatic challenges such as surgery, trauma or childbirth since history may not be informative in the absence of a sufficient hemostatic challenge. Patient questionnaires and clinical risk assessment tools such as the International Society of Thrombosis and Hemostasis Bleeding Assessment Tool (ISTH BAT) can assist in risk stratifying patients and guiding evaluation.<sup>2,3</sup> A patient with a family history of significant hemorrhagic complications should be evaluated for increased bleeding risk. Complete drug and medication histories (including homeopathic or herbal remedies) are important to evaluate for agents that affect platelet function or the clotting cascade. The physical examination should look for petechiae, excessive bruising as well as hepatosplenomegaly or spider naevi that may indicate liver disease, or joint effusions and other stigmata of previous bleeding.

## Laboratory Testing

An abundance of laboratory tests are available for the evaluation of hemostasis. Therefore, one must adopt a systematic approach to selecting which, if any, laboratory studies a particular patient requires.

### Risk-Stratified Approach to Laboratory Testing

In 1983, Rapaport devised the following four-level stratification scheme to determine the need for preoperative laboratory testing according to the patient’s clinical status and bleeding history (Table 39.1), and the planned operation<sup>4</sup>:

#### Level I

Patients who have no bleeding history and will undergo minor procedures, such as lipoma excision. No further hematologic evaluation is required because the cost of testing outweighs the probability of finding an abnormality and the risk of bleeding and because testing that is not indicated may inappropriately delay surgery.

**TABLE 39.1****Risk Stratified Approach to Preoperative Hemostatic Assessment**

Risk level	Findings	Recommended testing
Level 1	Negative history and physical examination for a proposed minor procedure	No further testing required
Level 2	Negative history and physical examination for a proposed major procedure	aPTT, PT and platelet count
Level 3	Suspicious history for major bleeding diathesis for a proposed major procedure	aPTT, PT, platelet count, and consider bleeding time or PFA-100
Level 4	Strongly suggestive history of a major hemostatic defect	aPTT, PT, platelet count, specific assays for factors VIII and IX, thrombin time, consider PFA-100 and consult with a hematologist

Adapted from Rapaport SI. Preoperative hemostatic evaluation: which tests, if any? *Blood*. 1983;61:229–231.

**Level II**

Patients who have no previous bleeding history but will undergo a major operation. This includes many patients undergoing open vascular operations that are potentially high risk for bleeding and involve intra- or postoperative anticoagulant or antiplatelet therapy that may increase bleeding risk. Normal prothrombin time, activated partial thromboplastin time (aPTT) and platelet count should effectively eliminate the risk of life-threatening bleeding.

**Level III**

Patients whose bleeding history raises concern for defective hemostasis and those in which the procedure may cause impaired hemostasis (e.g. use of high-dose heparin in cardiac procedures). In these patients, preoperative evaluation of the following factors is appropriate:

1. Adequacy of hemostatic plug formation – platelet count and bleeding time
2. Adequacy of coagulation reactions – prothrombin time (PT) and aPTT
3. Size and stability of the fibrin clot – factor XIII levels and fibrinolysis screening particularly in patients with a history of delayed surgical bleeding

**Level IV**

A history or physical findings highly suggestive of abnormal hemostasis, and the surgical procedure is not a factor. In addition to performing the tests indicated for level III patients, the following should be considered (especially if the results of level III testing are normal):

1. Factor VIII and factor IX levels
2. Thrombin time (TT) – to detect dysfibrinogenemia

3. Platelet function testing with the PFA-100 is useful to screen for vWD or impaired platelet function (preferred over bleeding time)
4. Bleeding time after the administration of 600 mg of aspirin – to uncover von Willebrand Disease (vWD) or a qualitative platelet disorder.<sup>5</sup>

**Proper Blood Drawing**

A properly drawn blood sample is paramount to interpreting the results of clotting tests; the specific methodology is beyond the scope of this chapter.<sup>6</sup> Whole blood is collected into an evacuated sample tube containing a fixed amount of citrate as an anticoagulant. The ratio of whole blood to citrate solution should be 9:1. An adult sample tube should be filled to at least 60% to 80% of its full collection volume to avoid excessive anticoagulation (a pediatric sample tube needs to be filled to 90% of its volume).<sup>6</sup> The anticoagulated blood should be mixed gently by being inverted three to four times. Testing should be done within 2 hours if the sample is kept at room temperature and within 4 hours if kept at 4°C. The screening tests used to determine the cause of coagulopathy are summarized on Table 39.2.

**Specific Laboratory Tests****Prothrombin time**

PT is used to assess the extrinsic pathway of clotting (factor VII) as well as the common pathway (factors II, V, X and fibrinogen). The end point is the time required (in seconds) for a fibrin clot to form. Vitamin K antagonists such as warfarin prolong PT. Argatroban therapy and very high doses of heparin can also cause an elevated PT value secondary to thrombin (IIa) inhibition.<sup>7</sup>

**Activated partial thromboplastin time**

The aPTT is used to assess the intrinsic pathway (factors VIII, IX, XI, and XII) and final common pathway (factors II, V, and X and fibrinogen) of clotting. Primary uses of aPTT include monitoring heparin therapy and detecting lupus anticoagulant, hemophilia A (factor VIII deficiency), and hemophilia B (factor IX deficiency). Table 39.3 lists the causes of prolongation of PT, aPTT, or both.

**Thrombin time**

TT measures the conversion of fibrinogen to fibrin, which is the final step in the clotting pathway. Prolongation of TT is attributable to direct thrombin inhibitor (DTI) therapy, heparin, lytic administration, disseminated intravascular coagulation, and dysfibrinogenemia.

**Activated blood clotting time**

The activated clotting time (ACT) test is performed by addition of a coagulant-accelerating matrix (e.g., diatomaceous earth) to a sample of whole blood and measurement of the time required for clot formation. This method is generally used to monitor adequacy of heparinization in the operating room or interventional suite.

**TABLE 39.2** Tests of Coagulation and Clinical Uses

Test	Measured Variable	Causes of Abnormalities	Clinical Use
Prothrombin time (PT)	Factors II, V, VII, IX, and X; proteins C and S; tissue factor; fibrinogen	Consumptive coagulopathy, warfarin therapy, vitamin K deficiency, liver disease, deficiency of factors II, V, VII, IX, or X	Identify coagulopathy, monitor warfarin therapy
Activated partial thromboplastin time (aPTT)	All coagulation factors except factor VII and factor VIII	Consumptive coagulopathy, heparin therapy, lupus anticoagulants	Identify coagulopathy, monitor heparin therapy
Thrombin time (TT)	Fibrinogen (functional)	Consumptive coagulopathy, fibrinolysis, dysfibrinogenemia	Monitor fibrinolysis
Activated clotting time (ACT)	Global clotting function	Heparin use	Monitor intraoperative heparin therapy
Bleeding time (BT)	Platelet number and function	Abnormal platelet function, antiplatelet therapy, thrombocytopenia, uremia, von Willebrand Disease	Evaluate platelet function
Thromboelastography (TEG)	Clotting kinetics	Anticoagulants, platelet deficiency/dysfunction, fibrinolytics	Liver transplantation, monitoring during/after cardiopulmonary bypass
Fibrin degradation products (FDPs)	Fibrinolysis	Consumptive coagulopathy	Identify coagulopathy
Euglobulin lysis time (ELT)	Fibrinolysis	DIC, primary fibrinolysis	Monitor fibrinolysis, adjunct to diagnosing DIC or primary fibrinolysis

DIC, disseminated intravascular coagulation.

**TABLE 39.3** Causes of Prolonged PT and aPTT

Test Result	CAUSE OF TEST RESULT PATTERN	
	Inherited Causes	Acquired Causes
Prolonged PT and normal aPTT	Factor VII deficiency	Warfarin therapy Mild vitamin K deficiency Liver disease Disseminated intravascular coagulation
Prolonged aPTT and normal PT	Deficiency of factor VIII, IX or XI Deficiency of factor XII, prekallikrein or high molecular weight kininogen (not associated with bleeding) May be prolonged in von Willebrand Disease	Anticoagulants including heparin, argatroban, bivalirudin, dabigatran Lupus anticoagulant (not associated with bleeding) Acquired inhibitor (autoantibody) against factor VIII, IX, XI, XII or vWF
Both PT and PTT prolonged	Deficiency of factor II (prothrombin, X, V or fibrinogen) Combined factor deficiency	Severe vitamin K deficiency Disseminated intravascular coagulation Liver disease Acquired factor X deficiency in amyloidosis Acquired inhibitor of factor II (prothrombin, X, V or fibrinogen)

### Bleeding time

The bleeding time, or the time needed for a superficial wound to clot, is used to assess primary hemostasis. One measures bleeding time by making a controlled wound in the forearm or earlobe and subsequently measuring the time for clotting to occur.<sup>8</sup> Clotting that takes longer than 5 minutes is considered abnormal. Bleeding time is mainly affected by the number and function of platelets, although vasoconstriction or vasodilation may affect the bleeding time as well. Other factors that prolong the bleeding time include heparin therapy (as a result of platelet inhibition), vWD, thrombocytopenia, aspirin or other antiplatelet therapy, and uremia. The bleeding time was widely used in the past to predict surgical bleeding but has become less popular in recent practice since it is difficult to standardize and does not appear to predict the safety of surgical procedures.<sup>9</sup>

### PFA-100

The PFA-100 is a point of care assay to evaluate primary hemostasis. Citrated whole blood is exposed to high shear stress by aspirating it through cartridges that have an aperture within a membrane coated with either collagen and epinephrine (CEPI) or collagen and ADP (CADP). These agonists along with high shear stress induce closure of the aperture by a platelet plug. Closure time (CT) is measured, and prolongation of CT with one or both agonists is a sensitive screening test for aspirin effect, functional platelet defects or vWD. It is important to note that in addition to aspirin and nonsteroidal anti-inflammatory drugs, other medications such as common antidepressants may also affect PFA-100 closure times.

## Thromboelastography and rotational thromboelastometry

Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are point of care tests which measure real-time clot characteristics, including formation and dissolution kinetics, as well as *in situ* fibrinolysis.<sup>10</sup> Due to rapid turnaround time for these tests, they are useful for intraoperative monitoring of anticoagulation (e.g., cardiac surgery) as well as in goal-directed hemostatic therapy in a bleeding patient after trauma, surgery, or post-partum hemorrhage.<sup>10–12</sup> There is emerging data to support the use of TEG/ROTEM to guide blood product administration in patients on extracorporeal membrane oxygenation (ECMO).<sup>12</sup> Future studies may establish the utility of TEG/ROTEM for guiding anticoagulation on ECMO, especially in the pediatric population.<sup>13,14</sup>

## Fibrin degradation products

Fibrin degradation products (FDPs) occur as the result of primary or secondary fibrinolysis. Elevations of their levels are seen in disseminated intravascular coagulation (DIC), cirrhosis, eclampsia, and trauma, and following lytic therapy. The FDP assay has few specific clinical applications except in the attempt to identify primary fibrinolysis.

## Euglobulin lysis time

The euglobulin lysis time (ELT) is an assay used to assess global function of the plasma fibrinolytic system. It measures the time required for a clot to lyse in a test tube (the normal value is 90–240 minutes). For this test to be useful, a patient must have adequate clot formation. This test is used as part of a panel to help differentiate a primary fibrinolytic state from DIC. A shortened ELT in patients without thrombocytopenia or schistocytosis is diagnostic of primary fibrinolysis, whereas a shortened ELT with thrombocytopenia or schistocytosis probably indicates DIC. ELT can also be used to determine the presence of excessive tissue plasminogen activator (t-PA) and deficiency of plasminogen activator inhibitor.<sup>15</sup> A drawback of this assay is its significant reported interlaboratory variability.<sup>16</sup>

## COAGULOPATHIES

Coagulopathy, or bleeding disorders, may be inherited or acquired and are classified as disorders of primary hemostasis or disorders of secondary hemostasis (Table 39.4)

### Inherited Coagulopathies

#### *von Willebrand Disease*

von Willebrand factor (vWF) plays an important role in primary hemostasis by binding to both platelets and endothelial components, effecting formation of an adhesive bridge between them. vWF also contributes to clot formation by acting as a carrier protein for factor VIII.<sup>17</sup>

von Willebrand Disease (vWD) is the most common inherited bleeding disorder. Although it affects about 1% of

**TABLE 39.4** Types of Coagulopathy

#### I. Disorders of Primary Hemostasis

Commonly present with mucocutaneous bleeding such as epistaxis, petechiae, etc. Bleeding after trauma or invasive procedures.

##### Inherited

Congenital platelet disorders including Glanzmann thrombasthenia, macrothrombocytopenias, storage pool defect von Willebrand Disease Connective tissue and vascular disorders (Ehlers–Danlos syndrome, Marfan syndrome, hereditary hemorrhagic telangiectasia, etc.)

##### Acquired

Acquired thrombocytopenia (immune thrombocytopenia, liver disease, drug-induced thrombocytopenia, hematological malignancy, etc.) Uremia Antiplatelet medications

#### II. Disorders of Secondary Hemostasis

Commonly present with joint, soft tissue, or internal bleeding. Bleeding after trauma or invasive procedures.

##### Inherited

Hemophilia A (factor VIII deficiency)  
Hemophilia B (factor IX deficiency)  
Rare inherited clotting disorders (deficiency of factor XI, X, VII, V, II and XIII)  
Congenital dysfibrinogenemia

##### Acquired

Acquired coagulation factor inhibitors  
Vitamin K deficiency  
Liver disease  
Anticoagulants  
Disseminated intravascular coagulation  
Amyloidosis associated coagulopathy  
Acidosis  
Dilution  
Hypocalcemia  
Hyperfibrinolysis

the population, only 5% of those affected are symptomatic.<sup>18</sup> Clinical manifestations range from none to severe bleeding, depending on the level of functional, circulating vWF. Easily identifiable but nonspecific symptoms include easy bruising, mucous membrane bleeding, prolonged epistaxis, postoperative bleeding, gastrointestinal bleeding, and heavy menstrual bleeding.<sup>19,20</sup> Previously undiagnosed patients sometimes have the first manifestation of the disease after taking antiplatelet agents such as nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin.

vWD is classified into three major types on the basis of clinical laboratory test results and genetic mutations, as delineated in Table 39.5. Type 2 comprises at least four subtypes with variable inheritance patterns. Patients with type 2A vWD ( $\approx 15\%$  of all with vWD) have decreased platelet-dependent functions owing to loss of high-molecular-weight multimers. Those with type 2B disease ( $\approx 5\%$  of all with vWD) have vWF with increased affinity for platelet glycoprotein Ib (GP-Ib). Type 2M is less common and results in reduced binding of vWF to platelet GP-Ib despite the presence of large vWF multimers. Patients with type 2N disease have mutations that alter the vWF binding site for factor VIII. Impaired binding effects rapid clearance of factor VIII.<sup>18</sup>

**TABLE 39.5** Types of von Willebrand Disease

Type	Transmission	Percentage of Cases of vWD (%)	Defect	Phenotype
1	AD	75	Quantitative deficiency of vWF	Mild–moderate bleeding
2	Autosomal but varied	20%	Multiple qualitative defects (2A, 2B, 2M, 2N)	Variable
3	AR	5	Absence/severe decrease in vWF	Severe bleeding

AD, autosomal dominant; AR, autosomal recessive; vWD, von Willebrand Disease; vWF, von Willebrand factor.

If vWD is suspected, the initial screening tests are (1) bleeding time or PFA-100, (2) closure time (vWF-dependent platelet function), (3) platelet count, and (4) aPTT. If results of these studies are positive or suspicious, more specific testing is pursued, which includes vWF antigen levels, ristocetin cofactor activity (assessment of vWF function), vWF antigen:ristocetin cofactor activity ratio, factor VIII activity, and blood type (type O is associated with lower vWF levels).<sup>17,21–23</sup>

Treatment decisions are based on severity of symptoms and type of vWD. Symptomatic patients should avoid NSAIDs. Desmopressin (DDAVP) is effective in patients with type 1 (and some type 2) vWD perioperatively and in those with mild to moderate bleeding episodes. Patients with type 3 and severe forms of type 2A, 2B, and 2M disease usually require replacement therapy with vWF, factor VIII–vWF concentrates, or cryoprecipitate. In general, the goal of treatment in these patients is to maintain the activity of factor VIII and vWF between 50% and 100% for 3 to 10 days to address episodes of serious bleeding or for major surgery.<sup>19</sup>

## Inherited Platelet Disorders

Inherited platelet disorders are rare conditions with varying degrees of phenotypic severity. These disorders affect multiple aspects of platelet function, namely aggregation, secretion, adhesion, and procoagulant activity. This group of disorders includes a large number of rare conditions, the most common of which are described in the following sections.

### Giant Platelet Disorders

Giant platelet disorders are a group of rare disorders characterized by thrombocytopenia, large platelets, and variable bleeding symptoms. They are generally subcategorized into four groups: those with a structural defect (e.g., Bernard–Soulier syndrome with glycoprotein abnormalities), those with abnormal neutrophil inclusions (e.g., MYH9-associated disorders), those with systemic manifestations (e.g., hereditary macrothrombocytopenia with hearing loss), and those with no specific abnormalities (e.g., Mediterranean macrothrombocytopenia).<sup>24</sup>

Bernard–Soulier syndrome, the most common of these platelet disorders, is characterized by thrombocytopenia, large platelets, and bleeding. It is attributed to dysfunction or absence of the GP-Ib/IX/V complex, which is a primary adhesion receptor of platelets.<sup>24</sup> The disorder manifests early in life with bleeding, most frequently epistaxis or gingival or cutaneous bleeding. Frequently, a severe hemorrhagic episode is noted after surgery (e.g., circumcision). Laboratory findings include

thrombocytopenia ranging from less than  $30$  to  $200 \times 10^3/\mu\text{L}$  (normal) and a prolonged bleeding time with normal clot retraction.<sup>24,25</sup> Management of patients with this syndrome usually entails education and avoidance of minor trauma. In the event of significant hemorrhage, platelet transfusion is indicated.<sup>26</sup>

### Glanzmann Thrombasthenia

Glanzmann thrombasthenia is an autosomal recessive disease with a large number of reported mutations. A defect in GP-IIb/IIIa renders platelets unable to aggregate.<sup>27,28</sup> Normal GP-IIb/IIIa allows platelets to bind soluble proteins and vWF. In Glanzmann thrombasthenia, platelets can attach to exposed endothelium but cannot form aggregates. A wide spectrum of phenotypic severity is reported, but mucocutaneous bleeding and the absence of platelet aggregation are classic findings.<sup>29</sup> Significant bleeding episodes typically require platelet transfusion.<sup>24,27,30</sup> Recombinant factor VIIa (NovoSeven) is also used to control bleeding in patients with Glanzmann thrombasthenia and other severe platelet function disorders, and is particularly useful in patients who cannot receive platelet transfusions due to alloimmunization or antibody formation against the missing platelet glycoprotein.

### Storage Pool Disorders

Storage pool disorders result from platelet granule deficiencies. The granules are usually divided into two groups: alpha granules (which contain vWF, thrombospondin, fibrinogen, and platelet-derived growth factor) and dense granules (which release adenosine diphosphate [ADP] and serotonin). Gray platelet syndrome is an example of an alpha-granule storage disorder.<sup>31</sup> This autosomal recessive disorder results in granules deficient in secretory proteins. Manifestations are typically limited to mucosal bleeding, but trauma-associated hemorrhage can occur. Laboratory analysis reveals moderate thrombocytopenia and a prolonged bleeding time. Preprocedural DDAVP and platelet transfusions form the basis for treatment. Dense-granule deficiencies include Chédiak–Higashi syndrome, Wiskott–Aldrich syndrome, and thrombocytopenia-absent radius syndrome.<sup>32</sup> Wiskott–Aldrich syndrome is an X chromosome-linked immunodeficiency manifested as thrombocytopenia with platelets of reduced size and function as well as eczema.<sup>33</sup> A defect in glycoprotein L115 (a leukocyte/platelet surface molecule) yields platelets that are unable to form aggregates.<sup>33,34</sup> Patients with the syndrome are typically diagnosed in early childhood with the constellation of thrombocytopenia, atopic dermatitis, and frequent infections. The only curative therapy is bone

marrow transplantation. If platelet transfusion is required prior to transplantation, HLA-selected platelets should be used and all blood products should be irradiated.<sup>34</sup>

## Hemophilia

The hemophilias are inherited bleeding disorders caused by deficiencies of specific coagulation factors.<sup>35</sup>

### *Pathogenesis*

The most common hemophilias are X-linked deficiencies of factor VIII (hemophilia A) and factor IX (hemophilia B).<sup>36</sup> Factor VIII is a complex plasma glycoprotein produced by liver sinusoidal endothelial cells and by vascular endothelial cells.<sup>37</sup> It has a half-life of 12 hours in adults and is protected from premature degradation by vWF. Factor IX is a vitamin K-dependent protein synthesized by the liver with a plasma concentration approximately 50 times that of factor VIII and a half-life of 24 hours.<sup>36</sup> Bleeding in hemophilia results from a failure of secondary hemostasis. Although a normal platelet plug forms, stabilization of the plug by fibrin is defective owing to inadequate amounts of thrombin.

### *Diagnosis*

Hemophilias A and B are clinically indistinguishable. Patients frequently present with joint bleeding or other soft tissue bleeding in response to minor trauma, or spontaneously. Patients with both hemophilia A and B exhibit prolonged aPTT but the diagnosis is confirmed by an assay for the specific factor. Depending on the concentration of the factor, hemophilia is classified as mild, moderate, or severe. Mild disease has a factor VIII or IX concentration between 0.05 and 0.40 IU/mL (5%–40% of normal) with bleeding manifestations after surgery, dental intervention, or trauma. Spontaneous bleeding is not seen. Moderate disease translates to a factor VIII or IX concentration of 0.01 to 0.05 IU/mL (1%–5% of normal). This concentration can result in bleeding into muscles and joints following minor injury. Major surgical or dental intervention effects severe hemorrhage.<sup>36</sup> Severe disease is seen with a concentration of factor VIII or IX of less than 0.01 IU/ml (<1% of normal).

Though most cases of hemophilia are identified via family history, some appear as *de novo* mutations. Whereas severe disease is typically diagnosed by 2 years of age, mild or moderate disease may not be recognized until adulthood. The hallmark of severe hemophilia A and B is spontaneous bleeding into joints and muscles.

Congenital deficiencies of other coagulation factors such as factor XI (hemophilia C), X, VII, V, II and XIII are exceedingly rare, and recessively inherited. Patients present with mucosal bleeding or bleeding at the time of invasive procedures although bleeding is variable and commonly less severe than in hemophilia A and B.<sup>38</sup>

### *Management*

The primary goal of treating hemophilia is to sufficiently increase the concentration of the missing factor to stop or prevent

spontaneous, traumatic, or surgical hemorrhage. Although DDAVP can sufficiently raise factor VIII levels in patients with mild hemophilia A, factor concentrations are typically required for more significant disease. Multiple factor VIII and IX concentrations are available as either recombinant or plasma-derived products. Prior to elective surgery, a factor VIII or factor IX level greater than 80% is recommended, with a goal of 30% to 50% to be maintained in the first two postoperative weeks.<sup>39</sup>

In some patients who undergo long-term replacement therapy, antibodies against factors VIII and IX develop. For these patients, recombinant factor VIIa (rFVIIa) or activated prothrombin complex concentrates might be necessary to achieve hemostasis. These agents act by bypassing the need for factors VIII and IX to achieve coagulation. The long-term goal for patients with high antibody titers is immune tolerance induction therapy, which results in a gradual reduction of antibody titers and increased tolerance of factor replacement therapy. Recently, emicizumab (Hemlibra®), a humanised monoclonal antibody that bridges activated factor IX (FIXa) and FX to restore activated FVIII (i.e. a nonfactor-based therapy), was approved for patients with hemophilia A. Emicizumab interferes with standard aPTT-based coagulation assays. If individuals receiving emicizumab prophylaxis require factor VIII infusions, the factor VIII activity must be measured using a bovine substrate-based chromogenic assay (bovine chromogenic factor VIII activity assay).<sup>40</sup> It is also important to note that unusual thromboses and thrombotic microangiopathy have been reported in patients with hemophilia with inhibitors on emicizumab prophylaxis who received activated prothrombin complex concentrates as a bypassing agent.<sup>41</sup>

## Acquired Coagulopathies

### *Platelet Disorders*

Acquired platelet disorders can result in quantitative or qualitative platelet deficiencies and should be considered in any investigation of abnormal bleeding, especially that accompanied by thrombocytopenia. Thrombocytopenia has myriad causes, including liver disease, cardiopulmonary bypass, hypersplenism, hematologic malignancy, medications, thrombotic thrombocytopenic purpura, immune thrombocytopenic purpura, etc. Other conditions such as uremia lead to a functional platelet defect.

Liver disease evokes thrombocytopenia via portal hypertension with splenic sequestration as well as by decreased thrombopoietin production. Cardiopulmonary bypass and mechanical assist devices place platelets in contact with nonphysiologic machine surfaces, which result in pathologic alterations in surface glycoprotein expression. Activation of these glycoproteins results in granule release as well as decreased endothelial adhesion and aggregate formation. Many acquired thrombocytopenias can be managed perioperatively with platelet transfusions. A notable exception is immune thrombocytopenia, one of the most common causes of isolated thrombocytopenia caused by immune platelet clearance. In immune thrombocytopenia, response to platelet transfusions is poor and preoperative treatment with intravenous immunoglobulin or corticosteroids to

improve platelet count is optimal. Thrombopoietin mimetics such as eltrombopag may also be used for perioperative management of immune thrombocytopenia.<sup>42</sup>

### **Uremia**

Although bleeding diatheses secondary to uremia are not completely understood, it is clear that platelet dysfunction plays a critical role. Uremia results in both intrinsic platelet defects and alteration of platelet–endothelial interaction.<sup>43</sup> Changes have been described in GP-IIb/IIIa, in ADP release from alpha granules, and in the arachidonic acid pathway.<sup>44</sup>

Uremic patients can exhibit easy bruising and mucosal bleeding. Laboratory evaluation demonstrates normal values for PT, aPTT, and platelet count. Directed treatment is typically reserved for major surgery or active bleeding, including correcting anemia to a hematocrit of 25% to 30% (to improve platelet aggregation and adhesion) and the administration of DDAVP (to enhance release of vWF) and/or conjugated estrogen (unknown mechanism).<sup>45</sup> Dialysis is the most effective treatment for uremic complications.

### **Vitamin K Deficiency**

Factors II, VII, IX, and X as well as proteins C and S require vitamin K for activation. Functional impairment of these factors is due to failure of vitamin K-dependent carboxylation. The cause is typically lack of vitamin K (malnutrition or malabsorption due to biliary obstruction or gut bacterial overgrowth) or pharmacologic blockade of vitamin K (warfarin). Treatment entails either functional factor replacement (with FFP or prothrombin complex concentrates) or vitamin K (allowing carboxylation of patient's factors) to address active bleeding or in anticipation of surgical intervention. Factor replacement with fresh frozen plasma (FFP) or activation prothrombin complex concentrates acts quickly as a direct replacement without the need for enzymatic reactions; it has an immediate effect that lasts about 6 hours. Vitamin K takes at least 6 hours to take effect but exerts a more durable reversal.

### **Disseminated Intravascular Coagulation**

DIC is systemic activation of the coagulation cascade that induces both thrombosis and hemorrhage.

#### **Etiology and pathogenesis**

DIC is always secondary to an inciting condition. The most common precipitants of DIC are sepsis, extensive traumatic tissue injury, cancer, amniotic fluid embolism, and placental abruption. The final common pathway for all of these entities is systemic activation of the coagulation cascade through multiple mechanisms that leads to uncontrolled production of thrombin, which leads to systemic intravascular deposition of fibrin. Proposed specific mechanisms are delineated in Table 39.6.<sup>46–49</sup>

Normally, thrombin generation is tightly regulated by a combination of intravascular and endothelial factors. In DIC, these inhibitory mechanisms become dysfunctional or overwhelmed, leading to uncontrolled microvascular thrombosis that causes the end-organ damage seen in severe DIC. The

**TABLE 39.6**

Mechanisms for Common Causes of Disseminated Intravascular Coagulation

Mechanism	
Sepsis	Extrinsic pathway Thrombin generation Suppression of protein C/thrombomodulin system <sup>39,39,140</sup>
Major tissue injury	Direct endothelial injury Release of phospholipids and enzymes to circulation
Malignancy	Expression of tissue factor by circulating tumor cells Procoagulant: calcium-dependent cysteine protease <sup>44</sup> Directly activates factor X

systemic thrombosis activates t-PA, which causes thrombolysis, consumptive coagulopathy, and bleeding diathesis. DIC exists in a spectrum ranging from acute (decompensated) DIC to chronic (compensated) DIC that represent two extremes of a pathogenic imbalance between coagulation factor and platelet consumption and production. Bleeding predominates in acute DIC, usually encountered in the setting of acute illness or clinical decompensation while chronic DIC is more likely to present with thromboembolic complications.<sup>50</sup>

#### **Diagnosis and management**

The diagnosis of DIC is based on a composite of simple, rapid tests of coagulation. DIC is characterized by prolongation of the PT and PTT, thrombocytopenia, drop in fibrinogen levels and elevation in markers of fibrin formation and degradation such as the D-dimer (Table 39.7). No single marker has adequately high sensitivity or specificity; normal values on any one of these markers does not rule out DIC and time-dependent longitudinal changes are most helpful in determining the presence of DIC. The ISTH has developed a composite scoring framework of global haemostatic tests, in which a score of  $\geq 5$  is indicative of overt DIC (Table 39.8).<sup>51</sup>

The overriding goal in the management of DIC is correction of the precipitating disease. Supportive therapy for acute DIC generally necessitates replacement of clotting factors and platelets while the inciting process is addressed. In patients with active bleeding, very aggressive replacement is pursued. Goals of resuscitation include a fibrinogen level over 100 mg/dL. Management also requires achieving and maintaining normothermia and adequate tissue perfusion. During the supportive phase, emphasis should be put on correcting the underlying pathologic process, the achievement of which will, in turn, stop the activation of the cascade. For instance, in septic patients, broad-spectrum antibiotics, abscess drainage, and debridement of infected or necrotic tissues is critical.

Anticoagulation with unfractionated heparin or low-molecular-weight heparin may be effective in chronic DIC with the thrombotic phenotype but has little utility in acute DIC where bleeding predominates.<sup>52,53</sup>

**TABLE 39.7**

## Coagulation Parameters in Disseminated Intravascular Coagulation

	Acute (decompensated) DIC	Chronic (compensated) DIC
Prothrombin time	↑	Normal/↑
Activated partial thromboplastin time	↑	Normal/↑
Platelet count	↓	Normal or ↓
Thrombin time	↑	Normal/↑
Fibrinogen	↓	Variable
Fibrin degradation products	↑	↑
D-dimer	↑	↑

DIC, disseminated intravascular coagulation; ↑, increased/prolonged; ↓, decreased.

**TABLE 39.8**

## International Society of Thrombosis and Haemostasis (ISTH) Score for Overt DIC

VARIABLE	Points
Platelet count, cells × 10 <sup>9</sup> /L	≥100
	50 to <100
	<50
Elevated levels of a fibrin-related marker (e.g. D-dimer, fibrin degradation products) using local lab cutoffs	No increase
	Moderate increase
	Severe increase
Prolonged PT, seconds	<3
	3 to <6
	≥6
Fibrinogen level, g/L	≥1
	<1

**Scoring**

<5: Not suggestive of overt DIC, may be non-overt DIC; repeat within next 1–2 days and manage clinically as appropriate

≥5: Compatible with overt DIC; treat for DIC as appropriate and repeat scoring daily

Adapted from: Taylor FB, Toh CH, Hoots WK, Wada H, Levi M. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *J Thromb Haemost*. 2001;85(5):1327–1330.

**Primary Fibrinolysis Disorders**

Fibrinolytic system derangements can result in either excessive bleeding or thrombosis. It is essential to differentiate primary fibrinolysis from secondary fibrinolysis (DIC) because of their differing management strategies. Plasminogen circulates as an inactive zymogen. Activation of plasminogen by t-PA or urinary-type plasminogen activator (u-PA) results in its conversion to plasmin, a serine protease that degrades fibrin. Inhibitors

of plasmin include plasminogen activator inhibitor (inhibits tissue and u-PA) and α2-antiplasmin (hepatic production). Thrombin-activatable fibrinolysis inhibitor (TAFI; a procarboxypeptidase activated by thrombin–antithrombin complex [TAT]) also constrains fibrinolysis by cleaving the C-terminal lysine residue of fibrin fragments. This disruption prevents recruitment of plasminogen to a partially digested clot, thereby inhibiting fibrinolysis (see Ch. 43, Thrombolytic Agents).

**Pathogenesis**

In this complex plasmin-plasminogen activator system, excessive bleeding can result from hyperactivity of plasminogen activators or deficient activity of fibrinolysis inhibitors. In primary fibrinolysis, there is pathologic direct activation of plasminogen. Excess circulating plasmin saturates plasminogen activator inhibitor-1 and α2-antiplasmin and cleaves fibrin and clotting factors, including factors V and VIII. Plasmin generated on the surfaces of platelets and endothelium inappropriately lyses hemostatic plugs. To counter the excess plasmin and fibrinolysis, excess thrombin is generated, resulting in microvascular thrombosis.

**Etiology/Diagnosis**

A primary hyperfibrinolytic state can develop in multiple clinical settings, including malignancy, liver failure, trauma, and congenital deficiency of fibrinolysis inhibitors.<sup>54,55</sup> Differentiating primary fibrinolysis from a secondary process, such as DIC, can be exceedingly difficult. The simplest laboratory findings to diagnose primary fibrinolysis are a short euglobulin lysis time in the absence of thrombocytopenia and the presence of schistocytes. Though challenging, the distinction between these two entities is critical as they require quite dissimilar treatments.

**Management**

The crux of treatment is the inhibition of fibrinolysis using antifibrinolytic agents. These lysine analogues, aminocaproic acid and tranexamic acid, act as competitive inhibitors of the conversion of plasminogen to plasmin.<sup>48</sup> Often, factor replacement is also required, typically factors V and VIII. Prior to its removal from the market, aprotinin was also used as a therapy for this disorder.<sup>49</sup>

**Drug-Induced Coagulopathies****Heparins**

Heparin is a naturally occurring, highly sulfated glycosaminoglycan. Heparin prevents clot formation and propagation by binding to and activating antithrombin. The resulting conformational change in antithrombin accelerates its ability to inactivate factors II (thrombin), Xa, and IXa.<sup>56</sup> Heparin can be monitored via ACT or aPTT, both of which demonstrate prolongation. In patients with baseline prolongation of the aPTT due to lupus anticoagulant, heparin-anti-Xa assays may be used to monitor therapy. Heparin is available for subcutaneous (half-life 8 hours) or intravenous (half-life 1.5 hours) administration. Intravenous heparin is frequently used for

intraprocedural anticoagulation because of its short half-life, point-of-care monitoring, and ease of reversal (protamine at 1 mg per 100 U intravenous heparin).<sup>49</sup>

Enzymatic depolymerization of unfractionated heparin results in fragments that are approximately a third the size of heparin. These are marketed as low-molecular-weight heparins (LMWHs; such as enoxaparin and fondaparinux). Administered subcutaneously, these agents offer a longer half-life and greater bioavailability than heparin.<sup>57</sup> Benefits of LMWHs include ability to be given once or twice daily and decreased need for laboratory monitoring for therapeutic use. The risk of bleeding with LMWH prophylaxis is low and is comparable to that seen with prophylactic subcutaneous heparin. Withholding fully therapeutic LMWH for 24 hours prior to major surgical intervention is recommended. There is no described benefit in protamine for reversal of LMWHs.<sup>58</sup> The use of either type of heparin risks heparin-induced thrombocytopenia. Briefly, patients with this disorder form antibodies to the complex of heparin and platelet factor IV on platelet surfaces. The presence of the antibodies leads to uncontrolled platelet activation and pathologic thrombosis (see Ch. 41, Anticoagulant Therapy).

### Thrombin Inhibitors

Intravenous DTIs include hirudin, lepirudin (recombinant hirudin), argatroban, and bivalirudin. The most common indication to use any of these agents is for the treatment of patients with heparin-induced thrombocytopenia. In contradistinction to heparins, these agents can bind to and inactivate clot-bound thrombin (a strong thrombogenic stimulus).<sup>59</sup> In comparison with heparins, DTIs have a more predictable response and are not impacted by acquired or inherent antithrombin deficiency (Table 39.9).

### Warfarin

Warfarin is an orally administered vitamin K antagonist (VKA). It acts by preventing vitamin K-dependent carboxylation of factors II, VII, IX, and X and of proteins C and S. The liver synthesizes nonfunctional forms of these proteins, which require carboxylation to become active. Following initiation, warfarin typically requires 2 or 3 days to take effect. Owing to the relatively shorter half-lives of proteins C and S in comparison with the clotting factors, a parenteral anticoagulant such as heparin or low molecular weight heparin is commonly required at the initiation of warfarin therapy to prevent sequelae of a paradoxically hypercoagulable state. The earlier loss of the anticoagulant effect of protein C or S (more commonly problematic in patients with protein C or S deficiency) can result in small vessel thrombosis, which manifests as warfarin-induced skin necrosis. This entity, if encountered, is treated with the cessation of warfarin and the initiation of therapeutic heparin.<sup>60</sup>

### Direct Oral Anticoagulants

Recently, direct oral anticoagulants (DOACs) that directly target the enzymatic activity of thrombin (dabigatran and ximelagatran) and factor Xa (rivaroxaban, apixaban, edoxaban) have been developed. Compared with warfarin, they

**TABLE 39.9** Intravenous Direct Thrombin Inhibitors

	Half-Life (min)	Monitoring Test	Disadvantages
Hirudin	40–50	aPTT	Expensive Narrow therapeutic window No antidote Problematic in renal dysfunction
Lepirudin	60–100	aPTT	Expensive Problematic in renal dysfunction Antigenic
Bivalirudin	25	aPTT Activated clotting time	Expensive
Argatroban	45	aPTT	Problematic in hepatic dysfunction Expensive

aPTT, activated partial thromboplastin time.

have a more predictable anticoagulant effect with fixed dosing and do not require frequent laboratory monitor and have food and drug interactions. The safety and efficacy of DOACs has been confirmed in randomized trials for multiple indications. These include perioperative prevention of venous thromboembolism (VTE), prevention of embolic events in atrial fibrillation, treatment of venous thromboembolism including in patients with cancer, thrombo-prophylaxis in major orthopedic surgery, and acute coronary syndrome.<sup>59,61–66</sup> However, DOACs are less effective than warfarin for the treatment of thrombosis in the antiphospholipid syndrome. Other indications for which warfarin is preferable to DOACs are the prosthetic heart valves, pregnancy, advanced liver disease since DOACs are hepatically metabolized to varying degrees, and altered gastrointestinal anatomy where absorption may be a concern.<sup>66</sup> Preliminary data on the safety and efficacy of dabigatran and rivaroxaban in pediatric patients is available, and clinical trials of these and other agents are ongoing.<sup>67</sup> Currently, the use of DOACs in children cannot be recommended outside a clinical trial.

DOACs also have shorter half-lives, which may aid in preoperative planning. Table 39.10 summarizes perioperative management of the DOACs.<sup>68</sup> Until recently, effective reversal agents were not available for DOAC-associated bleeding and nonspecific agents such as prothrombin complex concentrates and recombinant factor VIIa were used based on limited clinical data. Two specific antidotes, idarucizumab for dabigatran and andexanet alfa for direct factor Xa inhibitors, are now approved by the FDA and may be used for life-threatening bleeding when available. Adjunctive strategies for DOAC-associated bleeding include cessation of all anticoagulants, local management including mechanical compression surgical and radiologic intervention, and blood transfusion and hemodynamic support when required.<sup>69</sup>

**TABLE 39.10** Perioperative Management of Commonly Used Direct Oral Anticoagulants

Drug	Creatinine Clearance (mL/min)	Drug $t_{1/2}$ (hours)	TIMING OF LAST PREOPERATIVE DOSE (NUMBER OF DOSES SKIPPED)	
			Low Bleeding Risk Procedure (2–3 $t_{1/2}$ )	High Bleeding Risk Procedure (4–5 $t_{1/2}$ )
Dabigatran	>50	14–17	2 days (skip 2 doses)	3 days (skip 4 doses)
	30–50	16–18	3 days (skip 4 doses)	4–5 days (skip 6–8 doses)
Rivaroxaban	>50	8–9	2 days (skip 1 dose)	3 days (skip 2 doses)
	30–50	9	2 days (skip 1 dose)	3 days (skip 2 doses)
	15–29	9–10	3 days (skip 2 doses)	4 days (skip 3 doses)
Apixaban	>50	7–8	2 days (skip 2 doses)	3 days (skip 4 doses)
	30–50	17–18	3 days (skip 4 doses)	4 days (skip 6 doses)

$t_{1/2}$ , half life.

### Antiplatelet Agents

Commonly administered antiplatelet agents include aspirin, thienopyridines, clopidogrel, and ticlopidine. Aspirin irreversibly inactivates platelet cyclooxygenase with the resulting inhibition of platelet production of thromboxane A<sub>2</sub>. Clopidogrel and ticlopidine block platelet ADP receptors, effecting decreased GPIIb/IIIa expression. The duration of effect of all of these agents is 5 to 7 days because reversal requires the synthesis of new platelets.

Decisions regarding perioperative cessation of antiplatelet agents are frequent areas of debate. Most recent reports favor continuation of these agents when possible throughout the perioperative period. Ultimately, the determination depends on the indication for antiplatelet therapy as well as the extent of planned surgery and its attendant bleeding risk. Studies suggest that withdrawal of aspirin therapy in anticipation of coronary artery bypass grafting is associated with an elevated in-hospital mortality risk.<sup>65,70</sup> This finding was echoed in the analyses of the peripheral bypass population.<sup>71</sup>

Recommendations for patients with coronary stents who are taking clopidogrel are well-delineated. In this population, elective surgery should be postponed for at least 6 months for bare metal stents and 1 year for patients with drug-eluting stents in order to avoid interruption in therapy.<sup>72</sup> When therapy can safely be interrupted, cessation of clopidogrel or ticlopidine should occur 5 days prior to elective operation.

Abciximab and eptifibatide are antiplatelet agents that act via inhibition of GP-IIb/IIIa. Abciximab, frequently used during coronary procedures, is synthesized from Fab fragments of anti-GPIIb/IIIa immunoglobulins.<sup>73</sup> The result is inhibition of platelet aggregation. Platelet aggregation typically returns to normal 24 to 48 hours after cessation of therapy because of the agent's short half-life. Platelet transfusion can be used for emergency reversal because abciximab remains strongly bound to native platelets. Eptifibatide also decreases platelet aggregation and prolongs bleeding time.<sup>74</sup> It binds reversibly to GP-IIb/IIIa with a half-life of 2.5 hours. Platelet transfusion is not effective to reverse this agent.

A newer class of antiplatelet agents directly targets the platelet P2Y<sub>12</sub> receptor for ADP (collectively called P2Y<sub>12</sub> inhibitors).

Agents are available for intravenous (elinogrel, cangrelor) or oral (ticagrelor, elinogrel) administration. This alternative mechanism of action is important because about 30% of patients show inadequate platelet inhibition with clopidogrel therapy. The P2Y<sub>12</sub> inhibitors also have rapid onset and offset of platelet inhibitory action. This feature allows them to serve as a bridge therapy (when clopidogrel needs to be stopped in anticipation of an invasive intervention) as well as an alternative when clopidogrel fails. Although the efficacy of these agents is at least comparable to that of clopidogrel, there is some suggestion of higher bleeding complication rates with elinogrel (see Ch. 42, Antiplatelet Agents).<sup>75–77</sup>

### HYPOTHERMIA

Because coagulation factors are enzymes, their activity is substantially impaired by extremes of temperature or pH. Hypothermia in vascular surgery can result from insufficient ambient temperature, prolonged operative time, excessive blood loss, and the administration of cold fluid and blood products.<sup>78</sup> Results of laboratory studies can be falsely reassuring as the studies are routinely performed after sample warming to 37°C, which does not reflect the current patient condition.<sup>79</sup>

Maintenance of normothermia is critical during vascular procedures. Warming of inspired air can contribute significantly to maintenance of normothermia, increasing patient temperature as much as 3.5°C in 20 minutes.<sup>80</sup> Efforts to minimize the duration of the procedure and the extent of blood loss are also effective. Generally, active rewarming approaches, such as body cavity lavage, cardiopulmonary bypass, and continuous arteriovenous rewarming, are reserved for severe hypothermia related to trauma or submersion injuries.<sup>81</sup>

### ACIDOSIS

Acidosis impairs normal coagulation by reducing the activity of plasma proteases and coagulation complexes and cell surface interaction. For example, a pH decrease from 7.4 to 7.0 results in a reduction in factor VIIa activity by more than 90% and in factor VIIa-tissue factor complex by more than 60%.<sup>81,82</sup>

The most effective treatment of coagulopathy related to acidosis is to identify and address the underlying cause of the acidotic state. In sepsis, this process generally involves broad-spectrum antibiotics and aggressive drainage and/or debridement of infected tissue. If hypoperfusion is the cause of acidosis, volume repletion and inotropic support may be required. If reperfusion injury is anticipated, preemptive induction of respiratory and metabolic alkalosis prior to arterial clamp removal can reduce resulting acidosis.

## DILUTION

Coagulopathy secondary to dilution is common and is frequently overlooked. Large-volume resuscitation in the form of red blood cells (RBCs) or crystalloid or colloid fluids result in decreased plasma concentrations of coagulation factors and platelets. This relative depletion can lead to coagulopathy, especially in the setting of active bleeding. Some reports also suggest that hydroxyethyl starches, gelatins, and dextran solutions impair platelet function and interfere with fibrin polymerization. Hypertonic saline is also recognized to have anticoagulant and antiplatelet effects.<sup>83</sup> Experience from the military has emphasized dilutional coagulopathy in the setting of massive transfusion. Studies have also demonstrated the importance of high ratios of FFP to packed RBCs (PRBCs) and, to a lesser extent, of platelets to PRBCs to prevent this problem in trauma resuscitations.<sup>83,84</sup>

## TREATMENT OF BLEEDING

Treatment of clinically significant bleeding prioritizes therapies tailored to the etiology of bleeding and the maintenance of adequate perfusion. The surgeon should emphasize the determination of the cause of bleeding to appropriately tailor therapy. The currently available resuscitation and product replacement factors are summarized in Table 39.11.

### Packed Red Blood Cells

PRBCs are the most commonly transfused blood component. They are typically used to replace intraoperative or traumatic losses and to restore oxygen-carrying capacity. After blood donation, RBCs are separated out to create a concentrated product with 42.5 to 80 g of hemoglobin. The idea of a threshold hematocrit to trigger transfusion is debated. There is a move toward administering transfusion only in the presence of symptomatic anemia or ongoing or expected significant blood loss. The reasons for this paradigm shift are multifold. Studies have demonstrated that transfusing RBCs to a target hemoglobin of 7 g/dL rather than 10 g/dL did not adversely affect patient outcome.<sup>85,86</sup> In addition to concerns regarding infection transmission and transfusion reactions, data have been published describing problematic storage lesions in banked blood that may actually worsen patient oxygenation rather than improve it with transfusion.<sup>87</sup> There are also studies demonstrating

**TABLE 39.11** Blood/Coagulation Factor Replacements for Achieving Hemostasis

Resource	Dose and Effects	Product Content	Use
Packed red blood cells	1 unit (350 mL) increases hemoglobin level by 1g/dL (10 g/L)	Red blood cells	Symptomatic anemia (guideline hemoglobin level <6 g/dL if healthy), massive hemorrhage, decreased oxygen-carrying capacity
Platelets	1 unit (250 mL) increases the platelet count by 30,000–60,000/ $\mu$ L	Platelets, clotting factors	Thrombocytopenia, massive hemorrhage, platelet function deficit
Fresh frozen plasma	1 unit (250 mL)	All coagulation factors, especially factors II, VII, IX, and X, proteins C and S, and antithrombin III	Bleeding from warfarin therapy, massive transfusion, thrombotic thrombocytopenic purpura, coagulation factor deficiencies, antithrombin III deficiency
Cryoprecipitate	20 mL contains 200 mg fibrinogen, 70–80 units of factor VIII	Fibrinogen, factors V, VIII, and XIII, and von Willebrand factor	Hypofibrinogenemia, massive hemorrhage
Desmopressin	0.3–0.4 $\mu$ g/kg	Stimulates release of von Willebrand factor	Uremic platelet dysfunction, some von Willebrand Disease cases with bleeding
Vitamin K	10 mg intramuscularly, intravenously, or subcutaneously	Restores the function of factors II, VII, IX, X, protein C, and protein S	Liver dysfunction, bleeding from warfarin therapy
Protamine sulfate	1mg neutralizes 100 units of heparin	Heparin antagonist	Reversal of heparin therapy
Factor VII	50 $\mu$ g/kg (20–90 $\mu$ g/kg)	Recombinant factor VIIa	Hemophilia, massive hemorrhage
Aminocaproic acid	0.1g/kg loading dose, 1g/h	Plasminogen inhibitor	Primary fibrinolysis

significantly worse outcomes with a liberal compared to a conservative transfusion strategy. These outcomes include increases in postoperative infections, in-hospital mortality, lengths of stay in hospital and intensive care unit, and the duration of mechanical ventilation.<sup>86,88–92</sup> The American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies recommends that in otherwise healthy patients, hemoglobin levels be maintained at 6 g/dL (60 g/L) or above.<sup>93</sup> The adequacy of oxygen delivery must be assessed in individual patients, particularly those with limited cardiac reserve or significant atherosclerotic vascular disease. The initiation of transfusion should be based on developing signs of organ ischemia, the magnitude and rate of bleeding, and the patient's intravascular volume status.

## Platelets

Standard platelet transfusion doses are prepared by pooling concentrated platelets from whole blood donated by four to six patients. A unit of platelets approximately comprises 250 mL and  $3.5 \text{ to } 4 \times 10^{11}$  platelets. Such a dose is expected to increase the platelet count by 30,000 to 60,000/ $\mu\text{L}^3$ .<sup>94</sup> Single-donor apheresis platelets are also available. Potential advantages of these products include decreased risk of infectious transmissions and reduced alloimmunization. With the improvements in infection screening and leukoreduction techniques, these are likely no longer actual benefits and the use of the products simply increases the cost of platelet transfusion.<sup>95</sup> Generally accepted indications for platelet transfusion include prophylactic use in a patient with a platelet count less than 10,000/ $\text{mm}^3$ , and planned surgery or active bleeding in a patient with a platelet count less than 50,000/ $\text{mm}^3$ .<sup>96</sup> Early administration of platelets in massive transfusion treatment of major hemorrhage is also now recommended. Although not always possible, platelet transfusions should be avoided in patients with thrombotic thrombocytopenic purpura or autoimmune thrombocytopenias.

## Fresh Frozen Plasma

Plasma consists of the acellular portion of blood, which is separated and frozen after donation. FFP contains all coagulation factors. Accepted indications for its use are severe bleeding or a planned operation in a patient requiring replacement of multiple factors (as seen in liver disease or DIC); as part of a massive transfusion to treat or prevent dilutional coagulopathy; bleeding or the need for quick invasive intervention in a patient taking warfarin; and specific coagulation factor deficit for which no factor concentration or directed therapy is available. ABO compatibility is required.<sup>97</sup>

## Cryoprecipitate

Cryoprecipitate contains concentrated levels of fibrinogen, factor VIII, vWF, factor XIII, and fibronectin as well as platelet microparticles.<sup>98</sup> In the current era of factor concentrates, the primary indication for cryoprecipitate treatment is for

hypofibrinogenemia (often due to consumptive coagulopathy, primary fibrinolysis, or therapeutic thrombolysis).<sup>97</sup> A single unit of cryoprecipitate provides 150 to 250 mg of fibrinogen and 80 units of factor VIII.<sup>97,98</sup>

## Desmopressin

DDAVP is an arginine vasopressin analogue that stimulates release of vWF from the vascular endothelium.<sup>99</sup> Its initial uses focused on decreasing bleeding in patients with mild hemophilia A and vWD who required invasive interventions. Although the finding that DDAVP administration raises plasma levels of vWF and factor VIII seems to support this practice, extension of the practice to general use has not resulted in improved hemostasis.<sup>100</sup> A 2008 *Cochrane Database Systematic* update found no evidence that DDAVP decreased perioperative transfusion requirements or any other clinically relative outcomes in patients without congenital bleeding disorders. However, patients with specific congenital or acquired platelet disorders may benefit from this agent.<sup>100</sup>

## Vitamin K

Patients requiring operative intervention are not infrequently undergoing long-term oral VKA (warfarin) therapy (mechanism previously described). Whether vitamin K administration will offer adequate reversal of the effect depends on the urgency of the planned intervention. In a study of patients taking warfarin (international normalized ratio [INR] 1.4–1.9) administered 1 mg of oral vitamin K 1 day prior to surgery, 77% had INR values lower than 1.2 on the day of surgery.<sup>101</sup> However, vitamin K treatment by any route does not allow the immediate reversal required for more urgent or emergency interventions. These patients generally require FFP or prothrombin complex concentrates for rapid reversal of VKA effect.<sup>102,103</sup>

## Protamine Sulfate

Protamine sulfate is a small arginine-rich protein derived from salmon sperm nuclei. In order to reverse heparin effects, one administers 1 mg of protamine per 100 units of heparin administered in the last 6 hours. Protamine can cause a range of adverse reactions ranging from mild rash to life-threatening cardiovascular collapse. Previous exposure to protamine in this form or as neutral protamine Hagedorn (NPH) insulin predisposes patients to adverse reactions.<sup>104</sup> Vasectomy may also raise the risk of protamine-related events owing to the formation of antisperm antibodies via the exposure of blood to sperm (normally immunologically isolated in the testes). In a study of 243 patients undergoing cardiac surgery who received protamine sulfate, 26 had immediate protamine reactions; of these, 21 had previous protamine exposure (cardiac catheterization or surgery).<sup>105</sup> The precise mechanism of adverse protamine reactions is not well elucidated, but is believed to involve mast cell activation, complement activation, and antiprotamine antibodies. The most severe reactions are attributed to immunoglobulin G or E antibodies to protamine.<sup>104</sup>

## Factor VIIa

Recombinant factor VIIa (rFVIIa) (NovoSeven; Novo Nordisk A/S, Bagsvaerd, Denmark) was developed and is approved by the US Food and Drug Administration (FDA) for uses related to hemophiliac patients in whom antibody development limits the use of standard factor replacement therapies. Since its introduction, off-label uses of rFVIIa have steadily increased. Common off-label uses include cardiac surgery, trauma, and intracranial hemorrhage.<sup>106</sup> Although some reports suggest a decrease in transfusion requirement with its use, current evidence does not demonstrate reduction in mortality or other commonly measured outcomes in the off-label use of this agent. There also persists a concern regarding increased thromboembolic events associated with the administration of rFVIIa. Additionally, the cost associated with the use of this agent is not negligible; it is approximately \$7000 (USD) for a single 90 µg/kg dose.<sup>107</sup> Combat situations in which blood product supplies are limited may offer a reasonable off-label indication for rFVIIa. Recombinant factor VIIa is also used for patients with severe functional platelet disorders such as Glanzmann thrombasthenia and as a bypassing agent in patients with inhibitors against factor VIII or factor IX.

## Antifibrinolytic Agents

### Aminocaproic Acid and Tranexamic Acid

Lysine analogues such as aminocaproic acid (Amicar) and tranexamic acid prevent the conversion of plasminogen to active plasmin. A 2011 Cochrane Database review confirmed the role of lysine analogues in reducing perioperative blood loss and the need for allogeneic transfusion. The evidence analyzed in the review suggested greater efficacy for tranexamic acid than for aminocaproic acid.<sup>108</sup> These agents are reported to have good safety profiles and cost–benefit analyses when used for surgical patients with a high bleeding risk.<sup>109,110</sup> In the Clinical Randomization of Antifibrinolytics in Significant Haemorrhage 2 (CRASH-2) trial, early use of tranexamic acid, versus placebo, reduced bleeding related deaths (4.9% vs. 5.7%,  $P = 0.008$ ) and all-cause mortality at 28 days (14.5% vs. 16%;  $P = 0.0035$ ) without an increase in vascular occlusive events.<sup>111</sup>

## INTRAOPERATIVE BLEEDING

Intraoperative traumatic bleeding should be immediately managed with manual pressure. In the case of arterial bleeding, achieving proximal and distal control is a critical initial step allowing fastidious vascular repair. If there is a discrete source of bleeding, the need for pronged clamping of an artery, and no coagulopathy, systemic heparin can be administered.

The approach to venous bleeding is quite different because of the fragile, thin wall of the vessel and the more frequent extensive tributaries and branches. The risk of tearing or otherwise injuring veins is higher than for arteries and results in significant bleeding that can be quite difficult to control. Most small venous injuries can be adequately controlled with pressure, packing, or topical hemostatic agents. Extensive

collateralization of the venous system often allows more liberal ligation of these structures without significant clinical consequence in comparison with arteries. The following sections describe tools used for intraoperative hemostasis.

## Mechanical Tools

### Electrosurgery

William T. Bovie is the pioneer of electrosurgery (often inappropriately referred to as electrocautery, which would imply heating of a probe rather than heating of tissue).<sup>112</sup> He invented the prototype of the electrosurgical unit that was first used by neurosurgeon Harvey Cushing in October of 1926. The basis of electrosurgery is the finding that high-frequency current passes through the body, producing heat rather than evoking neuromuscular stimulation.

Electrosurgical unit settings include cutting and coagulation modes. The differences between these modes are in current continuity and voltage. The surgeon adjusts the mode (cut vs. coagulate) and power settings on the unit but cannot directly manipulate the current or voltage. For a given power setting, cutting mode minimizes the voltage but functions continuously, yielding a high current density that heats tissue very rapidly, resulting in vaporization. In contrast, the coagulate mode maximizes the voltage and applies the current in an interrupted fashion. This results in deeper tissue penetration with lower current density. The intermittent nature of the application generates less heat and produces a coagulum.

For monopolar electrosurgery, adequate sealing of the grounding pad is mandatory to prevent pad site burns resulting from increased current density over the reduced surface area caused by an insufficient seal. Alternatively, with very poor grounding pad application, the current can be directed to another site, such as electrocardiogram electrodes, resulting in burn injuries remote from the surgical field. A related caveat is that monopolar surgery should be avoided in locations with a limited cross-sectional area over which to spread the current (e.g., penis or finger). Monopolar electrodes are preferred, however, when deeper tissue heating is necessary.

When using bipolar devices, the surgeon grasps the target tissue between the tines of the forceps, allowing alternating current to flow from one tine to the other. This maneuver limits the production of heat to the small area of tissue grasped and effects the selective application of heat, avoiding injury to adjacent structures. Less power is required than for monopolar devices because the distance between the electrodes is significantly reduced. Bipolar devices are also effective in saline solution because of the smaller area of application. The LigaSure (Covidien AG, Boulder, CO) is a sealing device that combines bipolar electrocautery with pressure application designed to fuse collagen and elastin in vessel walls, producing a hemostatic seal.

### Argon Beam Coagulator

Monopolar devices can be enhanced by the addition of a stream of argon gas.<sup>113,114</sup> The column of argon gas passes over the tip of the electrode in a line with it. This arrangement adds several

functions: the fully ionized gas beam disperses pooled blood from the target area, allowing the electrical energy to have an effect where it otherwise would not. As a noble gas, argon also allows arcing of the current from the electrode along the gas beam to the target tissue, making possible diffuse coagulation of surfaces along the line of the argon column.<sup>113</sup> It is of particular use over raw bleeding surfaces, such as the liver or spleen.

### Radiofrequency Devices

The TissueLink device (Salient Surgical Technologies, Inc., Boston, MA) combines radiofrequency with continuous saline irrigation. It is designed to hemostatically seal cut bone and soft tissue.<sup>115</sup> The continuous and simultaneous application of saline is intended to decrease the temperature of the treated tissue, favoring mechanical sealing of the vessels rather than the coagulation and associated burning and charring seen with conventional electrosurgery.<sup>116</sup> The saline keeps the tissue temperature below 100°C (compared with up to 300°C seen with conventional devices). Luminal narrowing of target vessels is ascribed to collagen shrinking caused by the device.

The device is available in monopolar or bipolar forms for either spot application or painting of large raw surface areas. A disadvantage is the potential for “steam popping,” which can occur if the temperature of the subsurface tissue exceeds the desired 100°C despite a surface temperature of 100°C.<sup>117</sup> This complication may result in steam formation and tissue disruption. Constant moving of the probe over the target surface rather than continuous static application over a small area can prevent this complication.

### Topical Hemostatic Agents

Pusateri et al.<sup>118</sup> described the ideal topical hemostatic as (1) able to stop large vessel arterial and venous bleeding within 2 minutes of application to a wound even in a pool of blood, (2) ready to use without the need for special preparation or mixing, (3) simple to apply with minimal training, (4) lightweight and durable, (5) stable and functional for 2 years at room temperature and for several weeks at extreme ambient temperatures, (6) safe to use without the risk of injury to tissue or the transmission of infection, and (7) inexpensive. Though there is no single agent fulfilling all of these criteria, many advances have been made.<sup>119,120</sup>

### Mechanical Agents

#### Gelatin

Gelatin foam provides a physical matrix for clotting initiation and is available as Gelfilm and Gelfoam (both produced by Pfizer Inc., New York) in film, sponge, and powder forms. The powder is mixed with a sterile saline solution and applied as paste to sites of bleeding. Because Gelfoam paste is associated with less infection and inhibition of bone healing, it is a good alternative to bone wax for stopping bleeding from bony surfaces, such as a sternotomy incision.<sup>121</sup> It is important to note that Gelfoam swells more than collagen or cellulose products and can double its volume. Although this feature can enhance

mechanical hemostatic action, swelling can also cause compressive complications, especially when the product is used near nerves or in confined spaces. Gelatin foam is absorbed within 4 to 6 weeks and is largely nonantigenic despite its origin from animal products. Unlike oxidized cellulose, the pH of gelatin foam is neutral; therefore, it can be used in conjunction with thrombin or other pH-neutral biologics to enhance hemostatic action.

#### Oxidized Cellulose

Oxidized regenerated cellulose is branded as Surgicel Fibrillar and Surgicel Nu-Knit (both produced by Ethicon, Inc., Somerville, NJ). The material offers handling characteristics superior to those of gelatin foam, and the knitted fabric can be trimmed to fit any size. It does not stick to instruments and can easily be held firmly against bleeding tissue until hemostasis is achieved. Surgicel Fibrillar resembles cotton in consistency and remains pliable when laid into a wound. These products should not be moistened before use because greater hemostatic effect is exerted when they are applied dry.

Oxidized cellulose products result in a decreased local pH. There are theoretical advantages to this effect, including antimicrobial effects and hemostatic effects. Disadvantages of acidity include inactivation of other topical agents, such as thrombin (which should not be used together with cellulose), and potential increases in inflammation resulting in delayed wound healing.<sup>122</sup>

The observed discoloration of cellulose products following blood contact are attributable to low pH resulting in RBC lysis and hematin generation. Only the minimal necessary amount of product should be applied, with any excess agent removed after hemostasis is achieved.

#### Collagen

Microfibrillar collagen (MFC) is derived from bovine corium and available in several forms:

- A powder form, which is a fluffy, white-appearing dry material that conforms well to irregular surfaces: Avitene Flour (C.R. Bard, Inc., Murray Hill, NJ), Helitec (Integra LifeSciences Corporation, Plainsboro, NJ), and Instat (Ethicon, Inc.)
- A nonwoven sheet: Avitene and EndoAvitene (both C.R. Bard, Inc.)
- A sponge: Avitene Ultrafoam and Avitene UltraWrap (both C.R. Bard) and Helistat (Integra LifeSciences Corporation)
- A pad: Instat (Ethicon, Inc.)

Platelets adhere to the fibrils on the collagen's surface, resulting in activation and granule release. This results in platelet aggregation and thrombus formation with expected hemostasis in 2 to 5 minutes. Because this mechanism depends on functional platelets, its utility is limited in severe thrombocytopenia but retained in the setting of heparinization.

MFC should be applied with dry instruments because it adheres to gloves. It does not swell significantly, though adherence to neural structures should be avoided. Excess material should be removed after adequate hemostasis is attained. Blood from areas where this product is used should not be returned to the patient because the material may pass through the filters of blood-scavenging systems.

## Polysaccharide Spheres

The synthetic agents known as polysaccharide spheres – Arista (Medafor, Inc., Minneapolis, MN) and Trauma Dex – are designed to absorb plasma or blood and to concentrate clotting factors and platelets on their surfaces, forming a matrix that promotes clot formation. They require no preparation or delay for use. Disadvantages of these agents include a tendency to swell as well as a high sugar content, which limit use in closed spaces and in diabetic patients, respectively.

## Active Hemostatic Agents

### Thrombin: Liquid/Gel Products

Thrombin promotes the conversion of fibrinogen to fibrin and forms the basis of a fibrin clot. The original thrombin products used medically were of bovine origin; however, despite their reported efficacy, they demonstrated a tendency to result in antibody formation, which negatively affected outcomes in cardiac surgery as well as hemodialysis access (mostly involving coagulopathy and bleeding issues).<sup>123–126</sup> Recombinant human (Recothrom, The Medicines Company, Parsippany, NJ) and human plasma-derived (Evithrom, Ethicon, Inc.) thrombins were developed in response to these issues. In a phase II, randomized, double-blinded, comparative trial of topical recombinant human thrombin with bovine thrombin in surgical hemostasis, recombinant human thrombin was found to have comparable efficacy, a similar safety profile, and significantly less immunologic response in comparison with bovine thrombin.<sup>127</sup>

### Thrombin: Solid Products

TachoComb (NYCOMED Austria GmbH, Linz, Austria) is a collagen (equine) sheet coated on one side with human fibrinogen, bovine thrombin, and bovine aprotinin. The three components are distributed in layers that dissolve on contact with blood, allowing the formation of fibrin, which seals the wound by binding the collagen sheet to it.<sup>128</sup>

TachoSil (Takeda Pharmaceuticals International GmbH, Zurich) was developed in response to the realization that topical products containing aprotinin can have potential adverse effects, including anaphylaxis and renal injury. Therefore, TachoSil is made without aprotinin and with human rather than bovine-derived thrombin. This product is found to have equivalent hemostatic effects too, but has a lower risk of side effects than TachoComb.<sup>129</sup>

## Sealants

### FloSeal, Tisseel, Evicel

Fibrin sealants consist of two primary components that are mixed on application. Tisseel (Baxter International Inc., Deerfield, IL) combines human fibrinogen, human thrombin, and calcium chloride. Its mechanical strength is determined by the fibrin concentration. Thrombin concentration determines the speed of clot formation and tensile strength. This product does contain small amounts of aprotinin, which may carry the aforementioned risks of this agent. Evicel (Ethicon, Inc.) is a similar, later-developed product composed of fibrinogen and human-derived thrombin that lacks aprotinin.

FloSeal (Baxter International, Inc.) comprises a gelatin matrix of bovine collagen and microgranules cross-linked with glutaraldehyde and human thrombin.<sup>130,131</sup> The cross-linked gelatin granules swell on contact with blood, offering an additive tamponade effect. FloSeal was found to be superior to Gelfoam-thrombin in cardiac surgery and was shown to successfully reduce bleeding when used for open and laparoscopic nephrectomy.<sup>130,132</sup>

### Dry Fibrin Sealant Dressings

A dry fibrin sealant dressing consists of gauze embedded with lyophilized fibrinogen and thrombin. It is a solid-phase delivery mode for the clotting factors to promote and support clot formation. Its advantages include a long shelf-life and a lack of requirement for pre-mixing. Its use is limited in some forums by the brittle nature of the material.

### Tissue Glue

Several unique characteristics render tissue glues potential vehicles for drug delivery. They have a predictable pattern of biodegradability, can be applied in a site-specific manner, and are biocompatible.<sup>133</sup> BioGlue (CryoLife Inc., Kennesaw, GA) contains glutaraldehyde and bovine serum in addition to the tissue glue component. A scaffold is created by cross-linking of albumin to wound proteins.

## Newer Agents

### Chitins

The modified Rapid Deployment Hemostat (mRDH, Marine Polymer Technologies, Inc., Danvers, MA) bandage is a lyophilized matrix of acetylated, poly-N-acetyl glucosamine-containing nanofibers. The bandage rapidly binds and absorbs plasma proteins from blood. The nanofibers interact with receptors on platelets to stimulate activation and coagulation as well as agglutinating and activating RBCs. These interactions with platelets and RBCs result in the generation of thrombin and the deposition of a fibrin mesh. In addition to the formation of this hemostatic plug, thromboxane (from the activated platelets) and endothelin-1 (from endothelial contact with the bandage) effect vasoconstriction.<sup>134</sup> Case series from military use support the efficacy of this agent for at least temporary control of hemorrhage.<sup>129,135</sup>

### Chitosans

Chitosans are a deacetylated form of chitin. The gauze base of agents such as HemCon (HemCon Medical Technologies, Inc., Portland, OR) and TraumaStat (Ore-Medix, Salem, OR) contains silica and polyethylene, which interact with wound blood and coagulation factors to promote rapid hemostatic plug formation in a manner similar to that displayed by chitins.<sup>136</sup>

### Mineral Zeolite

Mineral zeolite agents such as QuikClot (Z-Medica, Wallingford, CT) function by absorbing water, an action that concentrates platelets and clotting factors to accelerate hemostasis. They may also activate factor XII. Multiple studies have demonstrated this to be a very rapid and effective manner to achieve hemostasis.<sup>137,138</sup> However, this mechanism is realized via an exothermic reaction that has been demonstrated to cause nontrivial

parenchymal thermal injuries in the region of application. A newer version, QuikClot Advanced Clotting Sponge, is intended to create a less exothermic reaction.<sup>136</sup>

### Lysine Analogues

The topical application of lysine analogues has been best studied in cardiac and orthopedic procedures. These antifibrinolytic agents act by preventing the binding of plasminogen to fibrin (thus countering the action of t-PA released from endothelial cells in response to surgical trauma). Of the four randomized, controlled, blinded studies of tranexamic acid in cardiac surgery, all showed less postoperative bleeding than with placebo;

only one demonstrated a reduction in the perioperative transfusion requirement. In orthopedic surgery, topical or intraarticular tranexamic acid similarly reduced blood loss. A sole study evaluated the use of aminocaproic acid in cardiac surgery. It demonstrated decreased blood loss in the first 24 postoperative hours (although accumulated loss prior to chest tube removal was not significantly different in the aminocaproic acid and the placebo arms) and a lower transfusion requirement in patients receiving aminocaproic acid. None of the studies evaluating topical lysine analogue use has been considered adequately tailored or powered to determine thrombotic or other potential risks (Table 39.12).<sup>120</sup>

**TABLE 39.12** Intraoperative Hemostatic Tools: Advantages and Disadvantages

Hemostatic Agent	Products	Mechanism of Action	Specific Advantages	Specific Disadvantages
<b>Mechanical Agents</b>				
Gelatin	Gelfoam Gelfilm Surgifoam (Ethicon, Inc.)	Matrix for clot formation Mechanical barrier to bleeding	Immediately available for use; stored at RT Can be used with thrombin/saline Conforms to wounds	Not for use in infected fields or near neural elements due to swelling risk Intravascular use should be avoided
Oxidized cellulose	Surgicel Surgicel NuKnit Surgicel Fibrillar BloodSTOP (LifeScience PLUS, Inc., Mountain View, CA)	Matrix for clot formation	Immediately available for use; stored at RT Small pieces easy to manipulate into small spaces	Not for use in closed spaces due to swelling risk Cannot be combined with thrombin
Microfibrillar collagen	Avitene Helitecne Instat	Matrix for clot formation/strengthening Enhances platelet activity	Immediately available for use; stored at RT	Not for use in closed spaces Cannot be combined with saline/thrombin
Polysaccharide spheres	Arista  TraumaDex (microporous polysaccharide hemospheres)	Hydrophilic effect dehydrates blood Concentrates solid components, resulting in barrier  Absorbs plasma-concentrating coagulation factors and platelets, forming gel matrix for clot formation	Immediately available for use; flexible storage temperature  No preparation	Not for use in closed spaces due to swelling risk Not for ophthalmologic, neurologic, or urologic procedures Limitations in diabetes due to sugar content of spheres  With sterilization, no risk of infection
<b>Active Hemostatic Agents</b>				
Synthetic or plasma-derived	Recothrom (recombinant human)  Evithrom (plasma-derived)	Actively converts fibrinogen to fibrin  Actively converts fibrinogen to fibrin	Stored at RT and reconstituted with saline	Cannot be used in patients hypersensitive to hamster/snake proteins  Frozen liquid form (takes at least 1 h to prepare) Contraindicated in patients with human blood product allergies
	TachoSil (equine collagen patch with human fibrinogen and thrombin)	Human thrombin converts fibrinogen to fibrin and polymerization yields coagulation effect; mechanical collagen effect	Stored at RT Patch placed directly on bleeding Modification of TachoComb (aprotinin should be avoided)	Human plasma-derived Infection risks Cannot be used in neurologic or urologic procedures
	TachoComb (sponge)	Collagen sheet, one side coated with human fibrinogen and bovine thrombin and aprotinin		Aprotinin content risks anaphylactic reactions and renal injury

*Continued*

**TABLE 39.12** Intraoperative Hemostatic Tools: Advantages and Disadvantages—cont'd

Hemostatic Agent	Products	Mechanism of Action	Specific Advantages	Specific Disadvantages
<b>Sealants</b>				
Polyethylene glycol	Coseal	Polyethylene glycol matrices cross-link in and with wound	Fast-acting Not exothermic	Not for use in closed spaces due to significant swelling
Fibrin sealants	Tisseel	Fibrinogen source	Does not need active bleeding to polymerize (prophylactic)	Frozen: 5–105 min to thaw
	Evicel	Fibrinogen source	No mixing required Does not need active bleeding to polymerize (prophylactic)	Frozen: at least 10 min to thaw Should be avoided in patients with known severe reactions to human blood products
Thrombin sealants	FloSeal (gelatin thrombin suspension)	Human and bovine thrombin formulation resulting in mechanical and active hemostasis contributions	3-min reconstitution Stored at RT	Should be avoided in ophthalmologic procedures
	Dry Fibrin Sealant Dressings (gauze embedded with lyophilized fibrinogen and thrombin)	Provides fibrinogen and thrombin	Has longer shelf-life than other sealants and does not require mixing	Brittle material causes handling and packaging issues
Bovine-derived factors	BioGlue (glutaraldehyde and bovine serum; glue)	Glutaraldehyde cross-links bovine albumin to wound proteins to make scaffold	Fast-acting Flexible use environment (temperature, moist)	Hypersensitivity reactions Theoretic mutagenic potential
<b>Newer Agents</b>				
Chitin	mRDH (Modified Rapid Deployment Hemostat) (gauze)	Mobilizes clotting factors, platelets, RBCs Mechanical sealant Vasoconstrictive	Very portable	No known significant adverse effects Gauze backing and small size <sup>113</sup> Varied results with severe injuries
Chitosan (deacetylated form of chitin)	HemCon, TraumaStat (granules) Chitogauze (HemCon Technologies), Celox (MedTrade Products Ltd., Crewe, UK), Hemogrip (Remedium Technologies, Inc., College Park, MD) (gauze)	Hemostatic plug forms on thrombin and fibrin mesh formed on gauze by receptor-based contact with RBCs and platelets	Antimicrobial properties Immediately available for use, stored at RT	No known adverse effects Cannot be used in patients with shellfish allergy Very user dependent
Mineral zeolite	QuikClot (combat gauze, granules, mesh bags)	Absorbs water from blood, thus concentrating platelets and clotting factors and promoting rapid local hemostasis Activates factor XII	Stored at RT, immediately available for use	Exothermic (burn) Foreign body reaction
Lysine analogues <sup>114</sup>	Tranexamic acid Aminocaproic acid	Antifibrinolytics block the binding of plasminogen to fibrin		

RBCs, red blood cells; RT, room temperature.

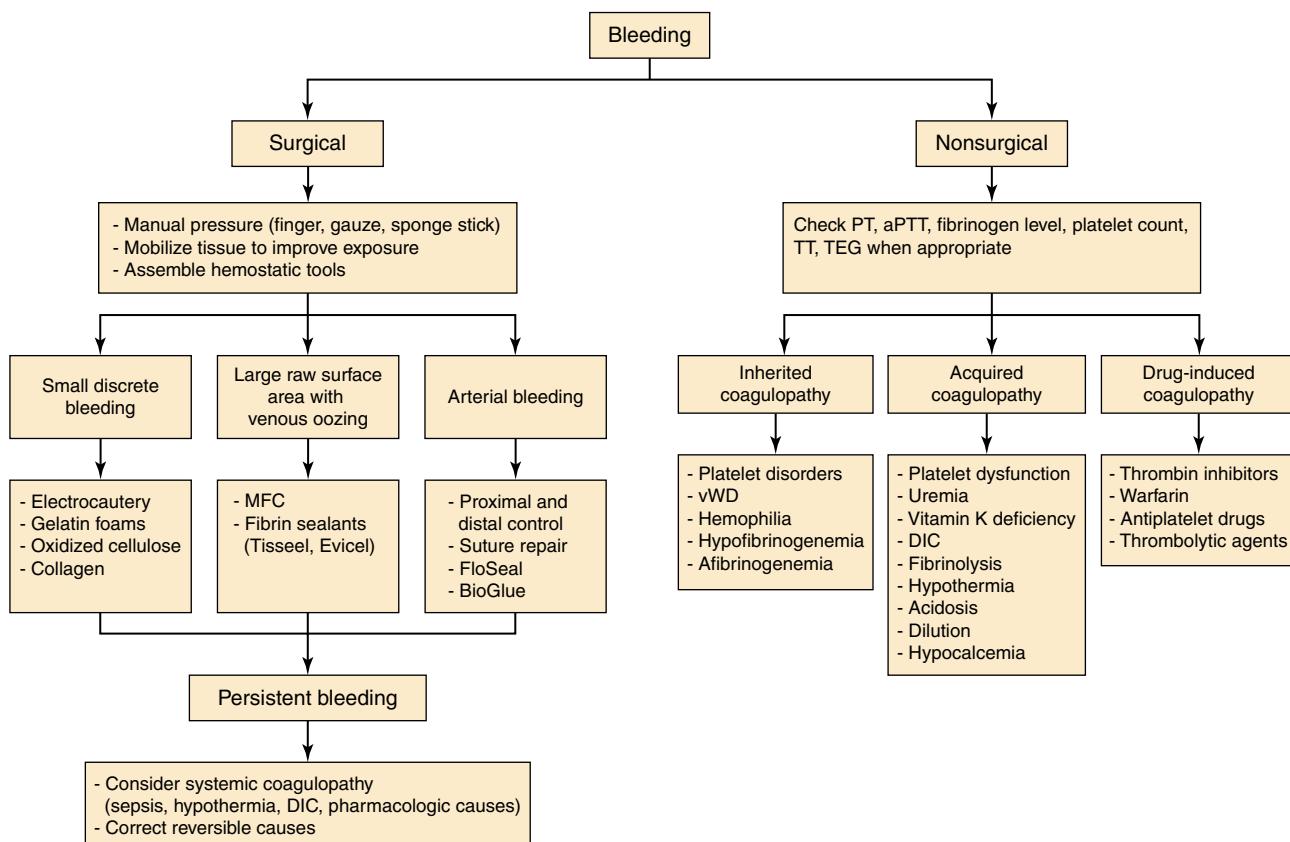
## POSTOPERATIVE BLEEDING

When patients demonstrate signs or symptoms of bleeding in the immediate postoperative period, a critical decision point is to determine whether it represents medical or surgical bleeding. Thus, while instituting aggressive, goal-directed resuscitation, the surgeon should be assessing the nature of the bleeding. Adjuncts in this process include coagulation parameters such as PT and aPTT, as well as the platelet count. If there is a suspicion or suggestion of consumptive coagulopathy, additional useful tests include fibrinogen, FDPs, and TT.

Management of postoperative bleeding hinges on its etiology and the severity. Severe surgical bleeding should be initially managed with manual pressure while the patient is transported back to the operating room. Here, small discrete bleeding may require a topical hemostatic, sutures, or a simple electrosurgery

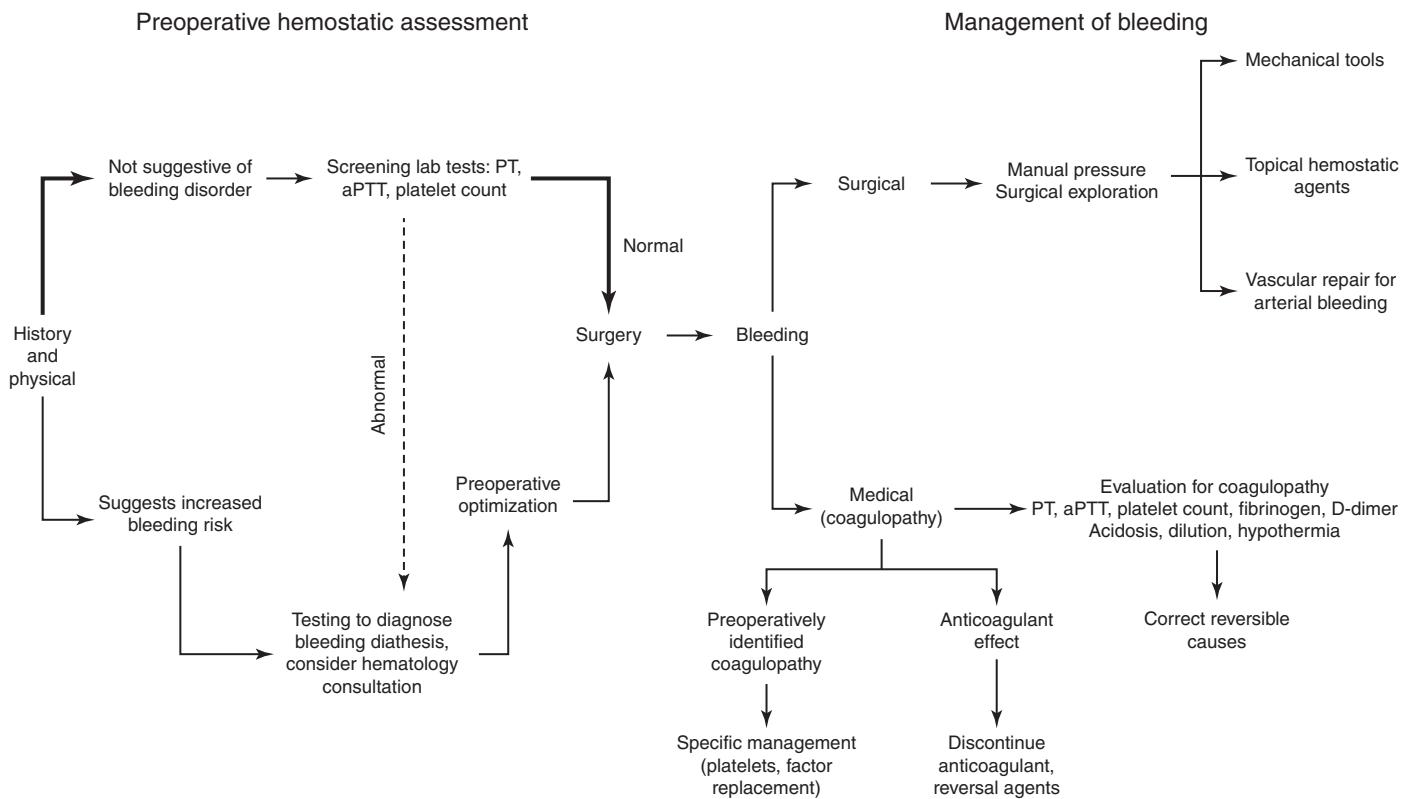
application. Large raw surfaces with venous oozing may be best managed with argon beam therapy or conventional electrosurgery application rather than a topical agent. Arterial bleeding is best addressed by rapid attainment of proximal and distal control followed by suture repair with or without the addition of topical agents.

Nonsurgical/medical bleeding is generally due to an isolated inherited or acquired coagulopathy or a diffuse coagulopathy related to surgery, sepsis, or massive resuscitation. Specific factor or blood element deficiencies can be treated with replacement. Drug-induced coagulopathies can sometimes be directly reversed. Homeostasis-related or diffuse coagulopathies require the correction of all involved factors, normothermia, and the correction of acidosis and dilution. Coagulopathy-related bleeding events are generally not best served by a return to the operating room. [Figure 39.1](#) summarizes the causes of and treatment strategies for perioperative bleeding.



**Figure 39.1** Causes and Management of Perioperative Bleeding. *aPTT*, activated partial thromboplastin time; *DIC*, disseminated intravascular coagulation; *MFC*, microfibrillar collagen; *PT*, prothrombin time; *TEG*, thromboelastography; *TT*, thrombin time; *vWD*, von Willebrand Disease.

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# Disorders of Coagulation: Hypercoagulable States

IAN SCHLIEDER and BENJAMIN S. BROOKE

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## INTRODUCTION

As first described by Virchow in 1856, the triad of hypercoagulability, vascular stasis and vascular trauma still remains the critical factors associated with vascular thrombosis.<sup>1</sup> Hypercoagulability causes abnormal thrombosis, which may occur in the venous or arterial circulation, as a consequence of both inherited conditions and/or acquired deficits. Different hypercoagulable states, also known as thrombophilias, may contribute to acute limb, or visceral ischemia, stroke, or cardiac thrombosis. As such, it is critical for vascular surgeons to be well versed with the contemporary diagnosis and management of hypercoagulable disorders.

The pathophysiology and molecular genetics of many thrombophilias have been elucidated over the past 50 years, and most can be managed using evidence-based algorithms. In most circumstances, the hypercoagulable state can be diagnosed by identifying the specific role the deficient factor plays in normal hemostasis. In addition, some individuals may have an inherited defect, but not develop a hypercoagulable state until they acquire an additional risk factor. This chapter provides a logical approach to the diagnosis and management of different hypercoagulable states.

## PATOPHYSIOLOGY

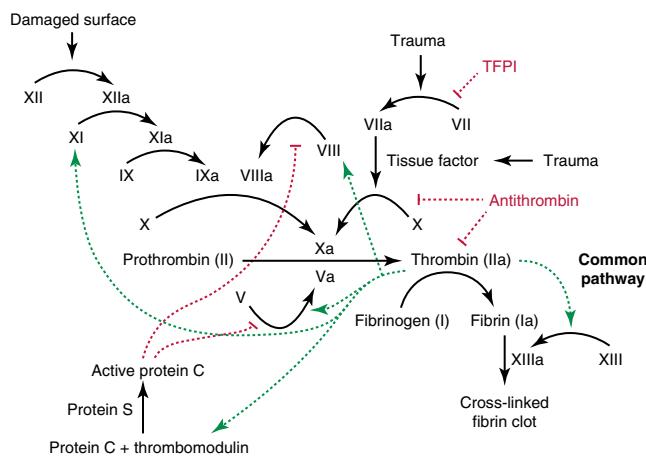
Coagulation is an inherent property of the hematologic system and blood vessel wall. Under normal conditions, the fluidity of blood flow is maintained by the balance between the procoagulant and antithrombotic factors contained within the blood and on the endothelial surface of the vessel wall. When endothelial injury occurs, primary hemostasis involves focal vasoconstriction from release of endothelin and secretion of von Willebrand factor, which initiates platelet adhesion and activation. Activated platelets secrete granules such as adenosine diphosphate, serotonin, and thromboxane A<sub>2</sub>, which in turn induces other platelets to congregate and form a platelet plug. If the vascular injury is small, the platelet plug may be able to form within several seconds and seal the injured area. But when a simple platelet plug is not enough to stop the bleeding, intrinsic and extrinsic pathways of the coagulation cascade are activated to help with clotting within a common pathway (Fig. 40.1). Secondary hemostasis is initiated from release of tissue factor, followed by activation of the coagulation proteins in a series of controlled enzymatic reactions that results in the generation of thrombin and cross-linked insoluble fibrin clot. However, there are also antithrombotic processes designed to counter the over-production of fibrin, involving the release of tissue plasminogen activator and thrombomodulin from the endothelium, and activation of antithrombin, and protein C and S (see Ch. 38, Normal Coagulation).

A hypercoagulable state may result from either overactivity of these endogenous procoagulant factors or a deficiency of the antithrombotic factors. This may result from a combination of genetic factors that are inherited and/or numerous environmental factors that an individual may acquire during their lifetime (Fig. 40.2). The interplay of genetic and environmental factors can result in biological effects that increase the risk for thrombosis. Further, hypercoagulability may also result from risk factors that primarily affect the vessel wall. This includes

### Intrinsic and extrinsic pathways of the coagulation cascade

Contact activation (intrinsic) pathway

Tissue factor (extrinsic pathway)



**Figure 40.1** Intrinsic and Extrinsic Pathways of the Coagulation Cascade. The coagulation cascade of secondary hemostasis has two initial pathways that lead to the common pathway of cross-linked fibrin clot formation via thrombin activation. This involves contact activation, also known as the intrinsic pathway, as well as activation of tissue factor through the extrinsic pathway. Coagulation factors are indicated by Roman numerals, with the lowercase “a” indicating an activated form of the protein. Platelet and coagulation factor activation are regulated at several levels of this cascade, including positive feedback (green arrows) and inhibition (red arrows) by protein C, antithrombin, or tissue factor pathway inhibitor (TFPI).

factors such as atherosclerosis, vasculitis, infection, or trauma that can contribute to endothelial disruption and activation of the coagulation cascade. As such, a patient's lifetime risk for thrombosis can increase by a factor more than the sum of each individual risk factor.<sup>2</sup>

## CONGENITAL HYPERCOAGULABILITY

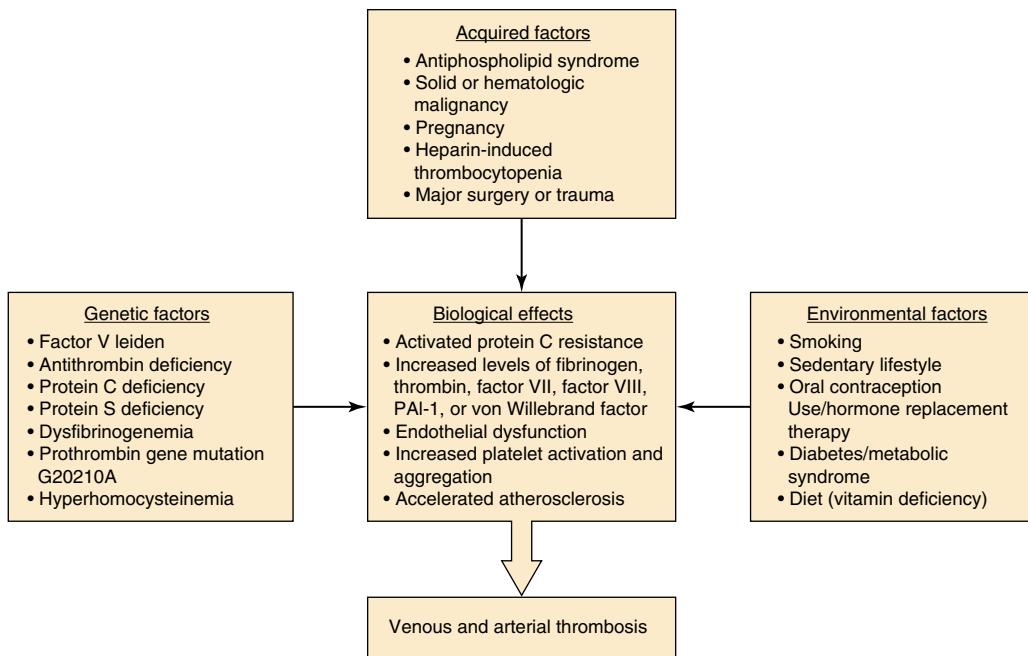
Congenital or hereditary hypercoagulability results from gene mutations in coagulation factors and can be divided into two broad groups using a simple classification system proposed by Crowther and Kelton in 2003 (Table 40.1).<sup>3</sup> Within this system, the first classification group is defined by defects that lead to reduced levels of the natural inhibitors of the coagulation cascade such as antithrombin, protein C, or protein S. These “loss of natural thrombosis inhibition” deficiencies are associated with a high risk of thrombosis during a patient's lifetime. The second classification group is associated with defects that result in a “gain in procoagulant function” due to increased levels or function of coagulation factors, including factor V Leiden or prothrombin G20210 mutations, increased levels of factor VIII, and the dysfibrinogenemias.

### Congenital Thrombophilia – Loss of Natural Thrombosis Inhibition

#### Antithrombin III Deficiency

##### Pathogenesis and incidence

Antithrombin III (AT3) is the most important inhibitor of thrombin and other activated clotting factors, including factors Xa, IXa, and VIIa. The physiologic activity of AT3 is enhanced



**Figure 40.2 Combination of Genetic, Acquired, and Environmental Factors that May Contribute to Hypercoagulable States.** The pathophysiology of thrombophilia is associated with risk factors that are inherited or acquired through biological events or environmental exposures. These factors, alone or in combination, are known to increase the risk for biological effects that cause venous or arterial thrombosis. PAI-1 indicates plasminogen activator inhibitor-1.

1000-fold by the binding of naturally occurring or administered heparin or heparin sulfates.<sup>4</sup> The incidence of inherited AT3 deficiency has been estimated at 1:2000 of the general population (Table 40.1).<sup>5</sup> Among individuals diagnosed with venous thromboembolism (VTE), however, AT3 deficiency has been reported to occur in between 4% to 7.5% of patients.<sup>6,7</sup> AT3 is inherited as an autosomal dominant trait, and more than 250 mutations have been described to date.<sup>8</sup> Nearly all patients are heterozygous for AT3 mutations, given that the severity of thrombophilia associated with homozygosity is rarely compatible with life.

### Subtypes

AT3 deficiency has been classified into two general subtypes based on how each gene mutation specifically affect antithrombin antigen levels.<sup>9</sup> Type I is characterized by point mutations or gene deletions that lead to low antithrombin antigen and activity levels.<sup>8</sup> In comparison, Type II mutations result from a mutation in the active inhibitory site on the protein that lowers functional antithrombin activity, but does not reduce its levels.<sup>8</sup>

### Clinical presentation

Patients with AT3 deficiency are at a significantly higher risk of venous thrombosis than patients with other hereditary thrombophilias. Approximately 60% of patients with AT3 deficiency will have a VTE event by the age of 60 years, and a family history of thrombosis is usually present.<sup>10</sup> The relative risk of VTE in patients with antithrombin deficiency has ranged between 10- to 30-fold within several large multicenter studies.<sup>2,11</sup> As

such, screening of first-degree family members is recommended after an AT3 deficiency diagnosis is made in an individual with VTE.

### Protein C Deficiency

#### Pathogenesis and incidence

Protein C is a vitamin K-dependent anticoagulation protein that is activated by thrombin to activated protein C (APC).<sup>12</sup> When thrombin levels are high, thrombin binds to the endothelial protein receptor, thrombomodulin (TM), which changes the specificity of thrombin from cleaving fibrinogen or activating platelets to activating protein C. Protein C binds to its specific endothelial receptor, termed the endothelial protein C receptor, which enhances its activation.<sup>13</sup> Mutations that result in deficiency of protein C are found in 0.2%–0.5% of the general population, and in 2.5%–6% of patients with VTE (Table 40.1).<sup>5,6,11</sup>

### Subtypes

Hundreds of mutations resulting in protein C deficiency have been reported to date.<sup>14</sup> The majority of people with protein C deficiency lack one copy of the functioning genes leading to activity levels less than 60%, whereas homozygous mutations are rare. These mutations have been classified into two general subtypes: type I mutations are considered quantitative defects and have reduced functional and antigenic protein levels of protein C. In comparison, type II mutations have reduced functional levels but preserved antigen levels of the protein. These are considered qualitative mutations that prevent protein

**TABLE 40.1** Epidemiology of Inherited Thrombophilias

Inherited Thrombophilia	Prevalence in General Population (%)	Frequency in Patients with VTE (%)	Relative Risk of Initial VTE	Relative Risk of Recurrent VTE
<b>Group 1 – Conditions That Lead to Loss of Natural Thrombosis Inhibition</b>				
Antithrombin III deficiency	0.02	4–7.5	10–30	3
Protein C deficiency	0.2–0.5	2.5–6	10	2
Protein S deficiency	0.1–0.7	1.3–5	10	1
<b>Group 2 – Conditions That Lead to Gain in Procoagulant Function</b>				
Factor V Leiden heterozygote <sup>a</sup>	2–7	10–19	3–6	1.1–1.8
Factor V Leiden homozygote <sup>a</sup>	0.06–0.25	1.5	7–20	2–3
Prothrombin G20210A heterozygote <sup>a</sup>	1–2	5–10	3–4	0.7–2.3
Prothrombin G20210A homozygote <sup>a</sup>	Rare	Unknown	2–20	Unknown
Elevated factor VIII	11	25	4.8 <sup>b</sup>	10–45 <sup>b</sup>
Hyperhomocysteinemia	5–10	10	2–4	1
Dysfibrinogenemia	Unknown	<1	Unknown	Unknown

VTE, venous thromboembolism.

<sup>a</sup>Heterozygous and homozygous carriers of the factor V Leiden and prothrombin G20210A mutations are predominantly found in patients of European descent.

<sup>b</sup>Relative risk of thrombosis depends on FVIII levels.

C from interacting with other molecules such as thrombomodulin, phospholipids, and factors V or VIII.

### Clinical presentation

Patients heterozygous for protein C mutations typically present with VTE involving the lower extremities. In comparison, homozygosity for protein C deficiency may result in nearly absent protein C activity and present at birth as a neonatal disorder termed purpura fulminans.<sup>15</sup> This disorder is characterized by diffuse microvascular thrombosis of the skin and systemic organs, and immediate treatment with heparin, plasma, or protein C concentrates are required to prevent neonatal death. The majority of homozygous neonates with protein C deficiency will have functional levels less than 20% of normal.<sup>15</sup>

### Protein S Deficiency

#### Pathogenesis and incidence

Protein S is the vitamin K-dependent cofactor necessary for the inactivation of factors Va and VIIa by APC.<sup>13</sup> Protein S exists in two forms: the functionally active free form that usually constitutes 20% to 40% of the total protein, and the remaining 60% to 80% that is active and bound to complement binding protein C4b.<sup>13,16</sup> Protein S deficiency can be found in up to 0.7% of the population and result from mutations that cause low levels of synthesis, increased proteolytic cleavage, and/or increased binding to C4b. Most patients with inherited protein S deficiency will have activity levels between 50% and 75% of normal.<sup>13</sup>

#### Subtypes

Protein S mutations can be classified into three different subtypes.<sup>17</sup> Type I mutations are characterized by reduced

functional and antigen protein levels of protein S. Type II has reduced functional activity of protein S, but normal antigen levels. And type III has normal antigen levels, but reduced free active protein S due to enhanced C4b binding. Type I and type III protein S deficiencies are the most common forms of the deficiency encountered.<sup>18</sup>

### Clinical presentation

A deficiency in protein S is phenotypically similar to protein C deficiency and patients typically present with VTE. However, protein S levels can also drop during the second and third trimesters of pregnancy, and woman may have fetal loss as their only manifestation of this disorder.<sup>19</sup> Reduced protein S levels have also been reported in patients with acquired conditions associated with thrombosis, which includes active cancer, lupus, antiphospholipid antibody syndrome, sepsis, inflammatory bowel disease, and advanced HIV disease.<sup>20,21</sup>

### Congenital Thrombophilia – Gain in Procoagulant Function

#### Factor V Leiden (aka Activated Protein C Resistance)

#### Pathogenesis and incidence

Factor V is a cofactor that accelerates the conversion of factor II (prothrombin) to thrombin by factor Xa. Under normal circumstances, factor V is degraded by the potent serine protease, activated protein C (APC). APC cleaves the protein at two sites, which helps modulate thrombin generation and subsequent clot formation. The most common mutation in factor V is a point mutation in the 506 position that results in a substitution of glycine for arginine (aka factor V Leiden).<sup>22,23</sup> This mutation renders one of the factor V

**TABLE 40.2**

Screening and Confirmation Tests Available for Evaluation of Congenital and Acquired Thrombophilias in Patients with Thrombosis

Thrombophilic Defect	Types of Screening Tests Available	Types of Confirmation Tests Available	Can Testing Be Performed in Setting of Acute Thrombosis
Factor V Leiden	Activated protein C resistance	Factor V Leiden genetic testing	Yes
Prothrombin G20210A	None	Prothrombin G20210A genetic testing	Yes
Antithrombin III deficiency	Antithrombin III functional assay	Antithrombin III antigenic assay	No
Protein C deficiency	Protein C functional assay	Protein C antigenic assay	No
Protein S deficiency	Protein S functional assay	Protein S antigenic assay	No
Elevated factor VIII	CRP and ESR levels	Factor VIII functional assay	No
Dysfibrinogenemia	Fibrinogen functional assay	Fibrinogen antigenic assay	No
Hyperhomocysteinemia	Fasting homocysteine levels	MTHFR genetic testing	Yes
Antiphospholipid syndrome	PT/aPTT levels Hexagonal phase phospholipid neutralization Anticardiolipin antibody assay	Lupus anticoagulant testing Dilute Russell's Viper Venom test Platelet neutralization procedure Incubated aPTT mixing study $\beta_2$ -Glycoprotein-1 antibody assay	Yes
Heparin-induced thrombocytopenia	Platelet counts Heparin/PF4 antibody assay	Serotonin release assay Heparin-induced platelet activation assay	Yes

MTHFR, methylenetetrahydrofolate reductase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PT, prothrombin time; aPTT, activated partial thromboplastin time.

cleavage sites resistant to the action of APC, and results in a slowing of the inactivation of the cofactor and increased thrombin generation. The factor V Leiden mutation is the most common inherited thrombophilia, occurring in approximately 2% to 7% of individuals of European ancestry.<sup>23</sup> It can be found in up to 19% of people with VTE and in 30% to 50% of individuals being evaluated for thrombophilia (Table 40.1). By comparison, the mutation is very rare in patients of Asian, African American, and Native American descent. Patients heterozygous for the factor V Leiden have a relative risk of thrombosis estimated at 3- to 6-fold, and a cross-sectional study from Italy found that only 6% of heterozygotes developed a thromboembolic event by the age of 65 years.<sup>2,7,24</sup> Homozygous carriers of this mutation have up to a 20-fold increased relative risk of VTE.<sup>25</sup>

### Clinical presentation

Patients with factor V Leiden mutations will typically experience VTE during adult years, and arterial thrombosis is rare. This risk will increase greatly if the patient is homozygous for this trait although the risk for thrombosis is still higher than the average population for heterozygotes. In the Physicians Health Study, the risk of VTE in men with a factor V Leiden mutation did not become statistically significant until after the age of 50 years.<sup>26</sup> The study also found no association between having the mutation and an increased risk of stroke or myocardial infarction. Thrombosis is frequently triggered by transient environmental or acquired risk factors, such as a prolonged plane flight, oral contraception (OC) use, or pregnancy.<sup>27</sup> In women carriers of the mutation, the reported thrombosis risk associated with the use of second-generation OCs varies widely, ranging from 6- to 50-fold.<sup>27-29</sup>

### Evaluation and testing

Testing for factor V Leiden mutations should only be undertaken if it will change patient management following an initial thrombotic event. There are several situations when it should be considered, which include: (1) patients with a history of an unprovoked VTE who are planning to stop anticoagulation; (2) female relatives of persons with a history of VTE or heritable thrombophilia who are considering hormone therapy such as OCPs or HRT; and (3) female patients with a family history who are planning to get pregnant and may need VTE prophylaxis. A recent assay developed to screen for APC resistance is performed by combining patient's plasma with factor V deficient plasma and a heparin neutralizer, and has nearly a 100% sensitivity and specificity for diagnosing factor V Leiden.<sup>30</sup> The diagnosis can be confirmed by determining a heterozygous or homozygous variant in genetic testing (Table 40.2).

### Prothrombin Gene Mutation G20210A

#### Pathogenesis and incidence

The prothrombin G20210A mutation is a defect located at the untranslated 3' end of the prothrombin gene, which affects the 5' end cleavage signal leading to increased prothrombin mRNA stability and plasma levels of prothrombin.<sup>31</sup> The frequency of this mutation is estimated to be between 1% to 2% in the general population and 5% to 10% of patients with a VTE event, with the greatest frequency in Caucasians from southern Europe or Spanish descent (Table 40.1).<sup>32-34</sup>

#### Clinical presentation

The majority of patients with the prothrombin G20210A mutation present with VTE of the lower extremities, and arterial

thrombosis is considered rare.<sup>34,35</sup> In carriers of this mutation who develop thrombosis, studies have shown that only a slight increase in risk of recurrent VTE occurs after discontinuation of anticoagulation.<sup>35</sup> However, the risk of thrombosis increases significantly when the G20210A prothrombin mutation is combined with other environmental or congenital risk factors. For instance, women taking OC therapy with the G20210A mutation have a significantly increased risk of VTE and are also at higher risk of developing cerebral vein thrombosis.<sup>36</sup> Further, the presence of both the G20210A prothrombin mutation and the factor V Leiden mutation increases the risk of recurrent deep venous thrombosis by a factor of 2.6, which mandates lifelong anticoagulation therapy.<sup>37</sup>

### Elevated Factor VIII Activity

#### Pathogenesis and incidence

Factor VIII is produced in the liver and 95% of the protein circulates in the plasma as a complex with von Willebrand factor (vWF), which protects it from inactivation by protein C.<sup>38</sup> The role of factor VIII in the coagulation cascade is activation of factor X, which directly participates in the generation of thrombin (see Fig. 40.1). Elevated factor VIII levels are found to cluster in families, although to date no specific mutations in the factor VIII gene that lead to high levels have been identified. Among patients in the 90th percentile with an elevated factor VIII activity >150%, studies have shown an increased relative risk of 4.8 for developing VTE (Table 40.1).<sup>39</sup>

#### Clinical presentation

High factor VIII levels are an independent risk factor for venous thrombosis of the lower extremities, but may also be associated with the risk of arterial thrombosis with other risk factors for atherosclerosis.<sup>38,40</sup> It has been suggested that factor III levels contribute to approximately 4% of arterial thrombosis cases, but there is controversy as to whether increased levels of factor VIII are independently associated with arterial thrombosis.<sup>38</sup> This uncertainty occurs because factor VIII levels are increased during inflammation and thus likely represent a cofactor in the development of thrombosis associated with infection, inflammatory bowel disease, and cancer.<sup>40</sup>

#### Testing

The measurement of factor VIII activity is confounded by the fact that factor VIII, along with its carrier protein, von Willebrand factor, is an acute phase reactant and increases with bleeding and inflammation.<sup>38</sup> Therefore, function assays used to measure factor VIII activity should be performed following measurement of acute phase marker, such as the ESR or C-reactive protein (Table 40.2).<sup>40</sup> These diagnostic assays should be repeated at least twice at distant time intervals, and each laboratory must define the 90th percentile range for its own population to determine the patient population at risk.<sup>39</sup>

### Hyperhomocysteinemia

#### Pathogenesis and incidence

Homocysteine is a non-proteinogenic amino acid that is an intermediary product in the metabolic conversion of methionine

to cysteine. Hyperhomocysteinemia is defined by abnormally high homocysteine levels in the plasma (above 15 µmol/L), and has been associated with the development of arterial vascular disease as well as venous and arterial thrombosis.<sup>41,42</sup> Multiple studies have shown that patients are predisposed to hyperhomocysteinemia by a relatively common mutation 677C→T in the methylenetetrahydrofolate reductase (*MTHFR*) gene when it is inherited as a homozygous trait.<sup>43</sup> The reported mechanisms by which homocysteine increases the risk of either arterial and venous thrombosis include: (1) a direct cytotoxic effect on endothelium; (2) enhanced platelet activation; (3) oxidation of low-density lipoprotein cholesterol; (4) an inflammatory decrease in endothelial TM; and (5) an increase in von Willebrand factor and factor VIII.<sup>43</sup> The prevalence of hyperhomocysteinemia is estimated to be 5%–10% in the general population, and up to 25% among those with vascular diseases (Table 40.1).<sup>42</sup>

#### Clinical presentation

Homocystinuria is a rare genetic disease leading to extreme hyperhomocysteinemia and is associated with the occurrence of arterial and venous thrombotic events at young age.<sup>44</sup> In adult patients, elevated homocysteine levels have been shown to increase the risk for myocardial infarction and stroke between 2- and 8-fold depending on other risk factors.<sup>45</sup> This is supported by data from the Physicians' Health Study,<sup>46</sup> the Atherosclerosis Risk in Communities Study,<sup>47</sup> and the Women's Health Study,<sup>48</sup> which all suggest that the risk is most significant for women with elevated homocysteine levels. In comparison, the association of hyperhomocysteinemia with VTE is more controversial. Nonetheless, a meta-analysis that included nine case-control studies demonstrated a significant association between hyperhomocysteinemia and a 3-fold increased likelihood of primary VTE.<sup>49</sup>

#### Testing

Hyperhomocysteinemia can be screened for using fasting serum homocysteine levels (Table 40.2). However, the measurement of homocysteine levels in patients can be complicated by comorbid conditions, such as vitamin deficiency or renal insufficiency. Measurements are best performed using freshly collected plasma, preferentially with patients in the fasting state. It is reasonable to repeat the assay on at least two separate occasions. With a high degree of suspicion, the diagnosis of hyperhomocysteinemia can be further confirmed based on the *MTHFR* genotype.<sup>50</sup>

### Dysfibrinogenemia

#### Pathogenesis and incidence

Fibrinogen is the precursor to fibrin and plays a key role in giving structure to clots, but also as a promoter of platelet aggregation and fibrinolysis. Although fibrinogen disorders are primarily considered to be bleeding disorders, they are also associated with thrombosis and can pose even higher risks than defects in other clotting factors.<sup>51</sup> One hypothesis for the increased risk of thrombosis is that concentrations of circulating thrombin are increased when fibrinogen is deficient.<sup>52</sup> Dysfibrinogenemias that

cause thrombosis can result from either hereditary or acquired abnormalities in the quantity and/or quality of circulating fibrinogens. Congenital dysfibrinogenemias are caused by mutations in the *FGA*, *FGB* or *FGG* genes.<sup>53</sup>

### Subtypes

Fibrinogen disorders are classified into two subtypes based on quantitative (type I) or qualitative (type II) defects.<sup>51</sup> A qualitative or functional fibrinogen disorder causes an abnormality in the fibrin molecule resulting in defective fibrin clot formation. In comparison, type II fibrinogen disorders are characterized by reduced fibrinogen antigen levels. Among patients with congenital dysfibrinogenemia, 40% of people have no symptoms, 50% have a bleeding disorder, and the remaining 10% have a hypercoagulable state.

## ACQUIRED CAUSES OF HYPERCOAGULABILITY

### Antiphospholipid Syndrome

#### *Pathogenesis and Incidence*

The antiphospholipid syndrome (APS) is one of the more common causes of acquired hypercoagulability, and is associated with an increased risk of both arterial and venous thrombosis.<sup>54,55</sup> The incidence of APS is approximately five cases per 100,000 persons per year.<sup>56</sup> APS is known to occur in conjunction with systemic lupus erythematosus (SLE), although 50% of patients do not fulfill criteria for SLE or other autoimmune disorders. The syndrome is characterized by the presence of antibodies that inhibit *in vitro* coagulation reactions known as lupus anticoagulant (LA), and antibodies that bind to anticardiolipin and  $\beta_2$ -glycoprotein.<sup>54,55</sup> Paradoxically, antiphospholipid antibodies prolong *in vitro* coagulation tests, most commonly, the activated partial thromboplastin time (aPTT), and the mechanism(s) by which they result in thrombosis remains unclear.<sup>57</sup> Activation of monocytes, platelets, and endothelial cells by antibody/ $\beta_2$ -glycoprotein-1 complexes have been implicated in the etiology of thrombotic events.<sup>58,59</sup> Antibodies to annexin II on endothelial cells, tissue plasminogen activator, and plasmin have also been proposed as additional antigenic targets. Further, complement (C5a)-mediated inflammation has been associated with increased thrombogenicity.<sup>57,58</sup>

There is strong epidemiologic evidence to support a relationship between the presence of antiphospholipid antibodies and thrombosis, with the highest risk of thrombosis associated with the presence of a LA and high titers of immunoglobulin-G (IgG) anticardiolipin antibodies.<sup>54,60</sup> This correlation was underscored by the results of the Leiden Thrombophilia Study, which found a 3.6-fold increased risk for deep venous thrombosis for individuals positive for LA.<sup>60</sup> Moreover, patients who were positive for both the LA and either antiprothrombin or anti- $\beta_2$ -glycoprotein-1 antibodies had an estimated 10-fold increased risk of VTE.

#### *Clinical Presentation*

Clinical criteria for APS include a history of either arterial or venous thrombosis and/or pregnancy complications with fetal

loss.<sup>54,55</sup> No laboratory test can distinguish patients at risk for either an arterial or venous event, although recurrent events most often recur in the sites of previous thrombosis. The risk of recurrent thrombosis may be as high as 50% in retrospective studies, while prospective clinical trials have estimated the relative risk of recurrence to be between 4- and 8-fold after stopping oral anticoagulants.<sup>61–63</sup> Professional consensus guidelines recommend indefinite anticoagulation for patients with APS and an associated thrombotic event.<sup>64</sup> Thrombosis at unusual sites is also well described with APS, including arterial emboli due to nonbacterial thrombotic endocarditis.<sup>65</sup> Finally, a severe variant of APS known as catastrophic APS (CAPS) is characterized by diffuse macro- and microvascular thrombosis with multiple organ involvement.<sup>66</sup>

#### *Evaluation and Treatment*

The 2006 Sydney Consensus statement is the most recent set of practice guidelines established for the work-up of APS, which recommend that both clinical and laboratory criteria be met before making the formal diagnosis.<sup>67</sup> Clinical criteria from these guidelines include: (1) unprovoked thrombosis of the venous or arterial system; (2) unexplained or multiple fetal loss after the 10th week of gestation; (3) premature births before the 34th week of gestation in the setting of pre-eclampsia; (4) eclampsia or recognized features of placental loss; and (5) three or more unexplained spontaneous abortions before the 10th week of gestation in the setting of maternal or hormonal abnormalities after maternal or paternal chromosomal causes have been excluded. Laboratory criteria require that two or more of the following be present in order for a diagnosis to be made: (1) lupus anticoagulant detected according to guidelines published by the International Society on Thrombosis and Hemostasis; (2) anticardiolipin antibodies exceeding 40 IgG or IgM antiphospholipid units; or (3) anti- $\beta_2$ GPI antibodies (IgG or IgM) at levels exceeding the 99th percentile, measured by enzyme-linked immunosorbent assay (ELISA). Additionally, these tests should be confirmed by repeating them twice at least 12 weeks apart.

Thrombosis in patient with APS has traditionally been treated with a vitamin K antagonist, and after the first unprovoked event anticoagulation should be continued indefinitely.<sup>68</sup> Several studies have looked at whether a higher INR target of 3.0–4.0 would help in refractory events for patients already on a VKA, but found no difference.<sup>69</sup> There has also been a lot of interest in determining whether direct-acting oral anticoagulants (DOACs) can be used safely to treat and prevent thrombosis in APS patients. A recent noninferiority clinical trial concluding that rivaroxaban was safe to use in lower risk APS patients.<sup>70</sup> However, a recent systematic review determined that the effectiveness of rivaroxaban may not be adequate in treating high-risk APS patients.<sup>71</sup>

### Solid or Hematologic Malignancies

#### *Pathogenesis and Incidence*

The etiology of thrombosis in patients with cancer is multifactorial, and may include increased expression of tissue factor by

**TABLE 40.3** Ottawa and Khorana Scoring Systems for Risk Prediction in Cancer Patients with Venous Thromboembolism

OTTAWA SCORE FOR PREDICTION OF RECURRENT VTE RISK IN CANCER-ASSOCIATED VENOUS THROMBOSIS		KHORANA SCORE FOR PREDICTION OF CHEMOTHERAPY-ASSOCIATED VENOUS THROMBOSIS	
Risk Factor	Points	Risk Factor	Points
Female Sex	1	Site of primary cancer	2
Lung Cancer	1	• Very high risk (stomach, pancreas)	1
Breast Cancer	-1	• High risk (lung, lymphoma, bladder, testicular, gynecologic)	
TNM Stage 1	-2	Pre-chemotherapy platelet count $\geq 350 \times 10^9/L$	1
Previous VTE	1	Hgb $< 10\text{ g/dL}$	1
		Pre-chemotherapy leukocyte count $\geq 11 \times 10^9/L$	1
		BMI $\geq 35\text{ kg/m}^2$	1
Interpretation	Total Score	Interpretation	Total Score
Low risk for recurrence	-3 to 0	Low risk of VTE	0
High risk for recurrence	1 to 3	Intermediate risk of VTE	1–2
		High risk of VTE	$\geq 3$

VTE, venous thromboembolism; TNM, Tumor Node Metastasis; Hgb, hemoglobin; BMI, Body Mass Index.

tumor cells as well as malignancy-induced inflammation resulting in prothrombotic changes in the vessel wall and increased levels of circulating fibrinogen, factor VIII, and platelets.<sup>72,73</sup> Additional prothrombotic risk factors frequently encountered by cancer patients include compression and invasion of vessels by tumors, the need for invasive surgical procedures, indwelling central venous catheters, and systemic chemotherapy.<sup>73,74</sup> The incidence of clinically significant VTE in cancer patients has been reported to range from 1% to 43%, depending on the type and stage of the tumor, the modality of cancer treatment, contributing risk factors, and other associated risk factors for thrombosis.<sup>72,75,76</sup> Patients receiving chemotherapy for metastatic disease are at a significantly higher risk of VTE, which may be 20-fold higher than patients without metastases.<sup>77</sup> Furthermore, the identification of subclinical pulmonary emboli among cancer patients at autopsy and by computed tomography scanning suggests that VTE remains an underdiagnosed phenomenon.<sup>78</sup>

### Evaluation and Treatment

There has been uncertainty about how to identify high-risk cancer patients who will require VTE prophylaxis, as well as what constitutes the optimal treatment strategy if these patients have a thrombotic event. Recently, two validated risk prediction models known as the Ottawa and Khorana scoring systems have been developed to help clinical decision-making in patients with cancer-associated VTE (Table 40.3). The Ottawa score is a clinical prediction tool designed to stratify patients according to their risk of VTE recurrence during the first 6 months of anticoagulation.<sup>79</sup> The Khorana score can be used to predict risk for VTE among patients on chemotherapy, and help select appropriate high ambulatory patients for thromboprophylaxis.<sup>80</sup>

The choice of anticoagulation therapy in cancer patients with VTE has been largely determined by the results of two

large open label RCTs. The CLOT trial randomized 676 patients to receive either the low-molecular-weight heparin (LMWH) agent dalteparin or warfarin for 6 months and found a significant reduction in symptomatic recurrent VTE associated with dalteparin with no difference in bleeding risk. These results were corroborated by the recent CATCH trial, where recurrent VTE was reduced among cancer patients randomized to the LMWH agent tinzaparin relative to warfarin.<sup>81</sup> Based on these findings, current guidelines recommend treating cancer-related VTE with 3–6 months of LMWH therapy or potentially indefinite treatment with active malignancy.<sup>82</sup>

The efficacy of using DOACs for the treatment of cancer-related VTE has been evaluated in several recent large studies. A prospective study of 1046 patients with cancer-related VTE treated with either oral edoxaban versus dalteparin for at least 6 months found no difference in recurrence rates between the treatment groups.<sup>83–85</sup> Further, the recent open label non-inferiority ADAM VTE trial randomized 1170 patients with cancer-related VTE to either apixaban or dalteparin and found similar VTE recurrence rates in both treatment groups at 6 months.<sup>86</sup>

### Pregnancy

#### Pathogenesis and Incidence

Pregnancy is known to induce an acquired prothrombotic state due to hormone-related elevations of fibrinogen and factor VIII as well as reduced protein S and depressed fibrinolysis.<sup>19,87</sup> Therefore, it is not surprising that the incidence of VTE is reported to increase 4- to 6-fold for pregnant females, and be even higher during the postpartum period.<sup>88,89</sup> The incidence is higher after cesarean section than vaginal delivery, and increases significantly among females with underlying inherited thrombophilia. Patients with congenital deficiencies of AT-III and proteins C or S are eight times more likely to

have thromboembolic complications during pregnancy as well antepartum thromboembolism compared to controls.<sup>90</sup> Data has suggested that up to 50% of Caucasian women with VTE at the time of the pregnancy could have an underlying thrombophilia such as a factor V Leiden mutation or a prothrombin G20210A mutation.<sup>90,91</sup>

### Evaluation and Treatment

VTE is the leading attributable cause of maternal mortality in the United States, representing 11% of maternal deaths.<sup>88</sup> As such, current guidelines suggest that all women be screened for risk factors that can increase the risk of a thrombotic event.<sup>92</sup> Depending on the number of risk factors present, a woman may be recommended LMWH either throughout the antenatal period, during the postpartum period or both. In particular, any woman with a prior unprovoked VTE event or known thrombophilia should receive LMWH prophylaxis during the postpartum period at a near (50%–75%) therapeutic dose or full dose for 6 weeks. For women diagnosed with VTE during pregnancy, therapeutic LMWH dosing is recommended with duration of therapy determined by the number of risk factors present.

## Oral Contraceptives and Estrogen Replacement Therapy

### Pathogenesis and Incidence

Estrogen used alone as hormone replacement therapy (HRT) or when used in combination with progestin in oral contraceptives (OCs) is a well-documented risk factor for both arterial and venous thrombosis.<sup>93,94</sup> While the exact molecular mechanism of estrogen-induced thrombosis remains unclear, it is likely mediated through its multiple effects on platelet activation/aggregation, the coagulation cascade, fibrinolysis and pro-inflammatory stimulation that tilt the hemostatic balance to a prothrombotic state.<sup>94</sup> The most common sites of thromboses for women on estrogen are deep veins of the legs, although there is also evidence that estrogen also increases the risk of arterial disease. A recent meta-analysis of 24 studies showed a 1.6-fold increased risk of MI or stroke for women taking OCs, which increased with higher estrogen doses.<sup>95</sup> For VTE, the increased risk appears to be highest during the first 4 months of starting OCs and returns to baseline within 3 months of discontinuing these agents.<sup>39</sup>

### Evaluation and Treatment

In the setting of acute VTE among women on OCs, therapeutic anticoagulation is not recommended beyond 3 months unless there is another anticipated estrogen challenge such as pregnancy.<sup>96</sup> However, the decision to withhold or continue OCs should take into consideration individual patient risk factors for thrombosis including family history, age, comorbidities, smoking history, and history of VTE. The use of OCs is contraindicated in women with a history of VTE, surgery with prolonged immobilization, and/or known congenital or acquired thrombophilia.<sup>97</sup> Further, OCs are contraindicated in women aged 35 or older who smoke and have cardiovascular

risk factors. Similarly, HRT use is contraindicated in women with previous VTE or stroke based on studies showing a 4-fold higher risk of thrombosis.<sup>98</sup>

## Heparin-Induced Thrombocytopenia

### Pathogenesis and Incidence

Unfractionated heparin (UFH) and LMWH use in vascular surgery is ubiquitous, and therefore the differential diagnosis of venous or arterial thrombosis in these patients must include consideration of heparin-induced thrombocytopenia (HIT). HIT is an immunologic disorder in which there is a polyclonal IgG antibody response against neoantigens expressed on platelet factor 4 (PF4) upon binding to heparin (heparin-PF4 complexes).<sup>99,100</sup> The larger heparin molecules contained in UFH induce larger PF4-antibody complexes, which may explain the greater incidence of HIT observed with UFH as opposed to LMWH or fondaparinux. Upon binding to the heparin-PF4 complex, the Fc domain of the HIT IgG antibodies activate platelets through the platelet Fc receptors, as well as induces tissue factor expression and cytokine release from monocytes and macrophages. These events result in HIT-related thrombosis, also referred to as HITT, which has been estimated to occur in 0.3% of patients receiving therapeutic doses of heparin during vascular surgery.<sup>100,101</sup>

### Clinical Presentation

Heparin-induced thrombocytopenia (HIT) is often suspected in patients with falling platelet counts after heparin administration, even if the heparin was discontinued.<sup>102</sup> The “4Ts” have been used as the starting point to determine the likelihood of a patient having HIT: (1) thrombocytopenia, (2) timing of thrombocytopenia in relation to exposure to heparin products, (3) thrombosis or other sequelae, and (4) likelihood of other causes for the thrombocytopenia. Thrombocytopenia characteristically involves a fall in platelet count  $\geq 50\%$  beginning 5–14 days after heparin exposure, with a nadir platelet count  $\geq 20 \times 10^9/L$ . Venous thrombosis predominates over arterial thrombotic events at a rate of 4:1, and there may be unusual manifestations such as skin necrosis at heparin administration sites or anaphylactoid reactions after heparin bolus. Finally, the diagnosis of HIT is supported when there are no signs of petechiae or bleeding normally seen in thrombocytopenia, as well as absence of other causes such as infection.<sup>100</sup>

### Evaluation and Treatment

There are two types of tests available for diagnosing HIT, including immunologic assays for screening and functional assays for confirmation (Table 40.2). Immunologic assays utilizing a PF4/heparin solid-phase enzyme-linked immunosorbent assay work by combining PF4/heparin or PF4/polyanion complexes with a patient's serum, and then observing whether IgG, IgA or IgM antibodies bind with the PF4 complexes. While the sensitivity of these immunologic assays is close to 100%, the specificity is between 50% and 89%. In comparison, functional

tests including serotonin release assays and heparin-induced platelet activation assays have a sensitivity and specificity >90% but are difficult to perform and relegated to only a few reference laboratories.

If HIT is suspected, all heparin and heparin-containing products should be immediately discontinued, including heparin flushes and any heparin-coated lines. Approximately 50% of patients with HIT characterized by thrombocytopenia alone will develop thrombosis if managed only with heparin discontinuation, and systemic anticoagulation is recommended to prevent other thrombotic complications.<sup>99,100</sup> In place of heparin, alternative anticoagulation agents include direct thrombin inhibitors (i.e. argatroban), direct Factor Xa inhibitors (i.e. apixaban), or indirect thrombin inhibitors (i.e. fondaparinux)<sup>100</sup> (see Ch. 41, Anticoagulant Therapy).

In patients who have developed HIT, surveillance for DVT with lower extremity venous duplex should be performed, as asymptomatic thromboses are common.<sup>103</sup> If thrombosis is identified, this event should be considered provoked and 3 months of anticoagulation therapy would be appropriate. Oral VKA therapy is typically used, although DOACs are now considered adequate for maintenance therapy. Most thrombotic events occur within 10 days of discontinuation of heparin, which corresponds with recovery of platelet function and number. As such, anticoagulation is recommended for a minimum of 10 days and up to a month depending on the perceived thrombotic risk.

After the initial instance of HIT, a key issue is whether it is safe for patients to have heparin products in the future, particularly those undergoing vascular procedures. Studies have shown that functional assays will become negative by 50 days after a diagnosis of HIT, and 60% of PF4/heparin antibody complexes become undetectable by 100 days.<sup>104</sup> When a vascular procedure needs to be performed, repeat functional and immunologic tests should be negative before heparin administration is given. If surgery is deemed urgent and cannot be delayed, then treatment with bivalirudin or argatroban intraoperatively is recommended.<sup>105</sup>

## EVALUATION AND WORKUP OF HYPERCOAGULABLE STATES

The evaluation of a patient presenting with an initial thrombotic event starts with a detailed history and physical evaluation. The etiology of arterial or venous thrombosis is typically multifactorial, and it is important to identify any defined risk factors or history that might suggest a hypercoagulable state. Nevertheless, the vast majority of patients with a thrombotic event will not be found to have a congenital or acquired thrombophilia. Patients presenting with arterial thrombosis typically will have established risk factors such as atherosclerotic disease, smoking history or diabetes mellitus.<sup>106</sup> Similarly, most patients are found to develop a “provoked” VTE in the setting of transient established risk factors, and current guidelines do not recommend thrombophilia testing for these patients.<sup>82</sup>

## Who Should Be Tested for Congenital and Acquired Thrombophilias

There have been no RCTs designed to guide decision-making among patients suspected of a thrombophilia, and recommendations are based primarily on epidemiologic studies.<sup>107</sup> Not every patient who experiences a thrombosis needs to be tested for a congenital or acquired thrombophilia. The diagnostic algorithm outlines who may benefit from testing and who may not after an initial thrombotic event. First, the clinician must determine if there are risk factors present that might explain why thrombosis has occurred. The presence of strong risk factors such as recent major surgery, trauma, or immobility would be sufficient to explain a VTE event, and testing should not be performed.<sup>107</sup> Conversely, the presence of weak transient risk factors in a patient of a certain age and/or family history might be sufficient to consider further workup and thrombophilia testing. For example, testing may be appropriate for patients with an arterial thrombosis that occurs before the age of 55 without established risk factors. Similarly, the occurrence of a VTE in a young patient with a strong family history or recurrent events would suggest that a heritable disorder may be present.<sup>108,109</sup>

Ultimately, a vascular provider’s decision to test for a thrombophilia should be based on the question of “Will the results of the test have the potential to benefit the patient and will it change their management?” Current evidence suggests that most of the time the presence of a thrombophilia will not change the management strategy for a VTE event.<sup>110,111</sup> Furthermore, routine testing has not been shown to impact patient morbidity or mortality outcomes.

However, there are a few specific circumstances when thrombophilia testing can change management, including patients with an unprovoked VTE. Given that the 5-year risk of recurrent VTE approaches 30% if long-term anticoagulation therapy is not given for unprovoked VTE, professional guidelines recommend extended anticoagulation therapy for these patients.<sup>112,113</sup> In this situation, thrombophilia testing can be of utility if it would change the duration of anticoagulation, or allow a provider to stop therapy completely for a given patient. But a negative test for thrombophilia in this setting should not lead the clinician to assume that the patient’s risk of recurrence is lower and stop anticoagulation early.<sup>107</sup>

Clinicians will also be confronted with scenarios whereby patients with unprovoked VTE want to know if their family members should be tested for congenital thrombophilias. At this time, guidelines recommend that asymptomatic family members of patients with VTE status should not undergo routine thrombophilia testing.<sup>107</sup> Family members in these situations, however, should be made aware of their increased risk and be given education on risk reduction strategies in high-risk situations.

Finally, there is debate about whether patients with thrombosis in unusual locations such as the splanchnic or cerebral veins should undergo testing for congenital or acquired thrombophilias. Recent evidence suggests that patients with unprovoked thrombosis in these locations could be at higher

risk of having a heritable thrombophilia, particularly factor V Leiden, and testing should be considered in the unprovoked setting.<sup>108,114</sup>

## Timing of Thrombophilia Testing

The timing of thrombophilia testing and workup should consider the most likely congenital or acquired condition based on a patient's history, as well as whether they are on anticoagulation therapy. Testing for factor V Leiden, prothrombin G20210A gene mutation or antibody titers for cardiolipin and  $\beta_2$ -glycoprotein can be performed at any time during an acute thrombosis event with accuracy (Table 40.2). Further, lupus anticoagulant assays can typically be performed accurately during the administration of heparin. However, testing for other congenital thrombophilic disorders will be inaccurate in this setting, and the recommendation is to wait until anticoagulation therapy has concluded.<sup>107,111,115</sup> As such, a two stage approach can be undertaken whereby a clinician can test for factor V Leiden and prothrombin G20210A mutations as well as the antibody titers for APS diagnosis during the first stage while patients are on anticoagulation. The second stage of testing occurs after anticoagulation has stopped, which may include assays for factor VIII, protein C, protein S, fibrinogen and AT3.<sup>107</sup> Finally, a hypercoagulable workup should not be performed while patients are on factor

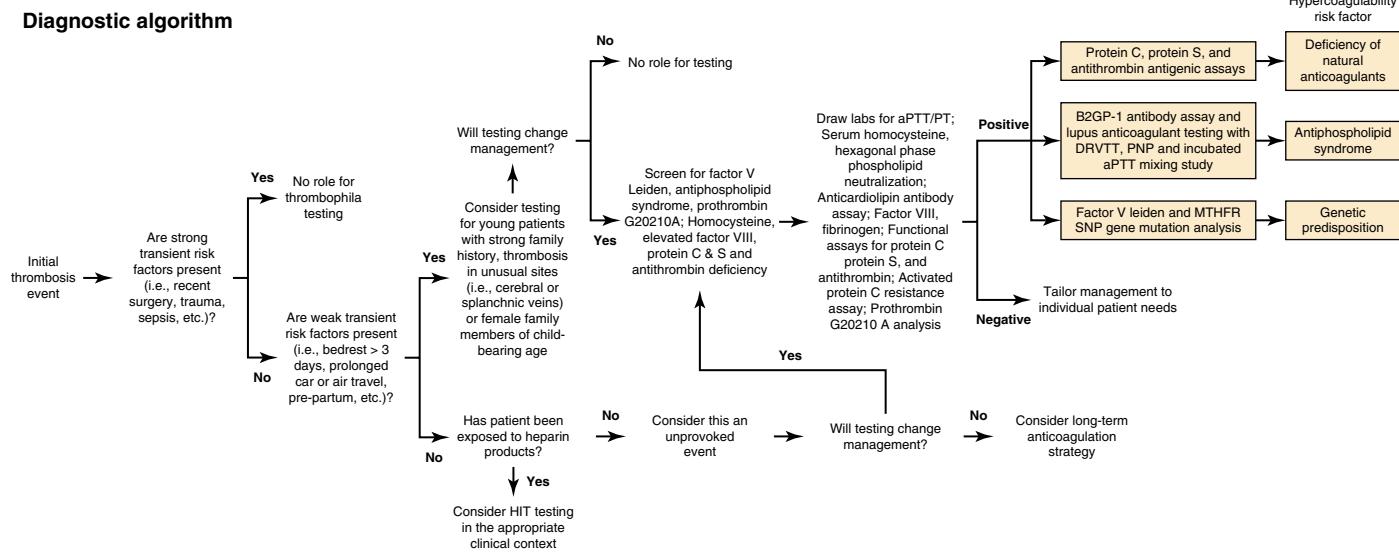
Xa inhibitors or direct thrombin inhibitors as these agents can invalidate some of the tests mentioned above.

## CHOICE AND DURATION OF ANTICOAGULATION THERAPY

For patients with either heritable or acquired thrombophilias, there are no specific guidelines regarding the choice or duration therapy for VTE events. In general, professional consensus guidelines published for the treatment of VTE can be applied in most clinical situations.<sup>82</sup> Moreover, therapy for VTE in most cases should be the same regardless of whether a heritable thrombophilia is present or not.<sup>111,113</sup> The majority of patients can be effectively treated with either a DOAC or VKA agent as first-line therapy, and the recommendation for patients in the provoked setting would be to treat for a 3-month period. For patients who have an unprovoked VTE event, anticoagulant therapy should be prescribed for an extended period of time or indefinitely unless their bleeding risk is prohibitive. If a patient is known to have cancer in the setting of a thrombophilia, the recommendation is to use LMWH for initial anticoagulation. If a patient has a recurrent event on either a VKA or a DOAC agent, then it is recommended that the patient be transitioned to LMWH. For failure while taking LMWH, the patient should have their dose increased by one-quarter to one-third.<sup>82,113</sup>

## CHAPTER ALGORITHM

### Diagnostic algorithm



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# Anticoagulant Therapy

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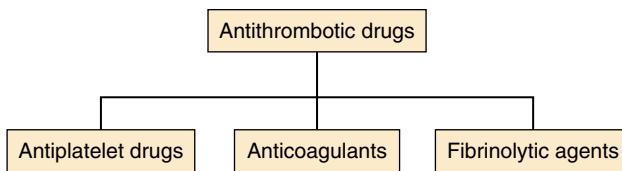
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## INTRODUCTION

Arterial and venous thromboses are major causes of morbidity and mortality. Arterial thrombosis is the most common cause of acute myocardial infarction (MI), ischemic stroke, and limb gangrene, whereas deep vein thrombosis can lead to pulmonary embolism, which can be fatal. Most arterial thrombi are superimposed on disrupted atherosclerotic plaque, which exposes thrombogenic material in the plaque core to the blood. This material then triggers platelet aggregation and fibrin formation, which results in the generation of a platelet-rich thrombus that can temporarily or permanently occlude blood flow.<sup>1</sup>

In contrast to arterial thrombi, venous thrombi rarely form at sites of obvious vascular disruption. Although they can

develop after surgical trauma to veins, or secondary to indwelling venous catheters, venous thrombi usually originate in the valve cusps of the deep veins of the calf or in the muscular sinuses, where they are triggered by stasis. Sluggish blood flow in these veins reduces the oxygen supply to the avascular valve cusps. Endothelial cells lining these valve cusps become activated and express adhesion molecules on their surface. Tissue factor-bearing leukocytes and microparticles adhere to these activated cells and induce coagulation.<sup>2</sup> In addition, webs of DNA released from activated neutrophils, so-called neutrophil extracellular traps, also contribute to thrombosis by providing a scaffold that binds platelets and promotes their activation and aggregation.<sup>3</sup> Local thrombus formation is exacerbated by reduced clearance of activated clotting factors as a result of



**Figure 41.1** Classification of Antithrombotic Drugs.

impaired blood flow. If the calf vein thrombi extend into more proximal veins of the leg, thrombus fragments can dislodge, travel to the lungs, and produce a pulmonary embolism.

Arterial and venous thrombi are composed of platelets and fibrin, but the proportions differ. Arterial thrombi are rich in platelets because of the high shear in the injured arteries. In contrast, venous thrombi, which form under low shear conditions, contain relatively few platelets and are predominantly composed of fibrin and trapped red cells.

Antithrombotic drugs are used for prevention and treatment of thrombosis. Targeting the components of thrombi, these agents include: (a) antiplatelet drugs, which inhibit platelets; (b) anticoagulants, which attenuate coagulation; and (c) thrombolytic agents, which induce fibrin degradation (Fig. 41.1). With the predominance of platelets in arterial thrombi, strategies for prevention or treatment of arterial thrombosis focus mainly on antiplatelet agents, although in the acute setting, they often include anticoagulants and thrombolytic agents. Anticoagulants are the mainstay of prevention and treatment of venous thromboembolism because fibrin is the predominant component of venous thrombi. Antiplatelet drugs are less effective than anticoagulants in this setting because of the limited platelet content of venous thrombi.

Anticoagulants are available in parenteral and oral forms. Parenteral anticoagulants include unfractionated heparin, low-molecular-weight heparin (LMWH), fondaparinux, a synthetic pentasaccharide, and parenteral direct thrombin inhibitors (bivalirudin, hirudin analogs and argatroban). Oral anticoagulants include vitamin K antagonists (VKAs), such as warfarin, and the direct oral anticoagulants (DOACs); dabigatran etexilate, which inhibits thrombin, and rivaroxaban, apixaban and edoxaban, which inhibit factor Xa.

This chapter focuses on anticoagulant drugs. The reader is referred to Chapter 42 (Antiplatelet Agents) for a comprehensive presentation of antiplatelet therapy.<sup>4–26</sup>

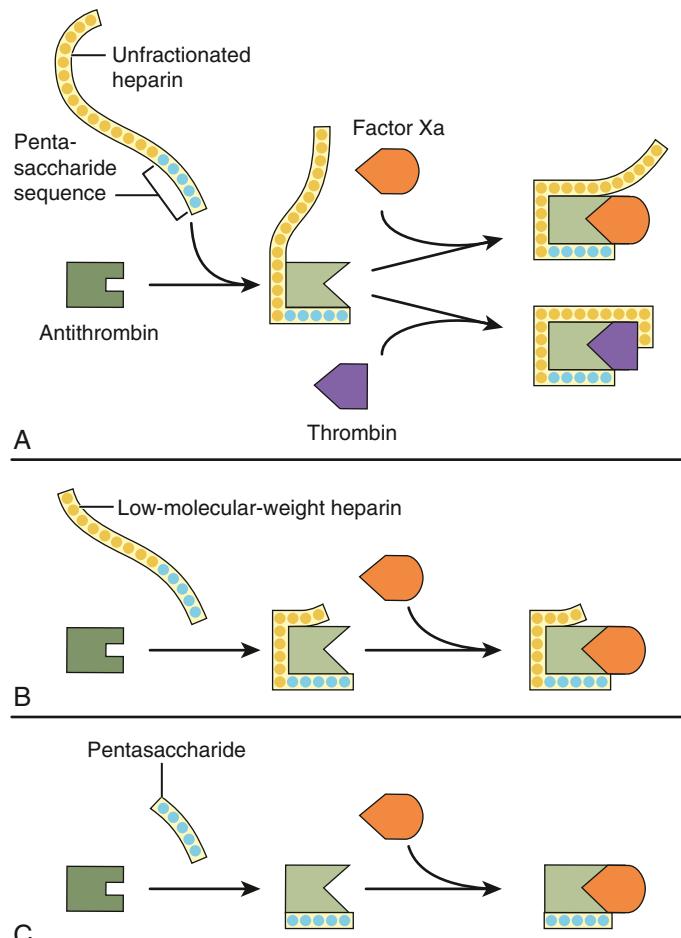
## PARENTERAL ANTICOAGULANTS

### Heparin

A sulfated polysaccharide, heparin is isolated from mammalian tissues rich in mast cells. Most commercial heparin is derived from porcine intestinal mucosa.

#### Mechanism of Action

Heparin acts as an anticoagulant by activating antithrombin (previously known as antithrombin III) and accelerating the rate at which antithrombin inhibits clotting enzymes, particularly thrombin and factor Xa. To activate antithrombin,



**Figure 41.2** Mechanism of action of heparin, low-molecular-weight heparin and fondaparinux, a synthetic pentasaccharide. (A) Heparin binds to antithrombin via its pentasaccharide sequence. This induces a conformational change in the reactive center loop of antithrombin that accelerates its interaction with factor Xa. To potentiate thrombin inhibition, heparin must simultaneously bind to antithrombin and thrombin. Only heparin chains composed of at least 18 saccharide units, which correspond to a molecular weight of 5400, are of sufficient length to perform this bridging function. With a mean molecular weight of 15,000, all of the heparin chains are long enough to do this. (B) Low-molecular-weight heparin has greater capacity to potentiate factor Xa inhibition by antithrombin than thrombin because, with a mean molecular weight of 4500 to 5000, at least half of the LMWH chains are too short to bridge antithrombin to thrombin. (C) The pentasaccharide only accelerates factor Xa inhibition by antithrombin because the pentasaccharide is too short to bridge antithrombin to thrombin.

heparin binds to the serine protease inhibitor via a unique pentasaccharide sequence that is found on one third of the chains of commercial heparin (Fig. 41.2). The remainder of the heparin chains that lack this pentasaccharide sequence have little or no anticoagulant activity. Once bound to antithrombin, heparin induces a conformational change in the reactive center loop of antithrombin that renders it more readily accessible to its target proteases. This conformational change enhances the rate at which antithrombin inhibits factor Xa by at least two orders of magnitude but has little effect on the rate of thrombin inhibition by antithrombin. To catalyze thrombin inhibition, heparin serves as a template that binds antithrombin and thrombin simultaneously. Formation of this ternary complex brings the enzyme in close apposition to the inhibitor, thereby

promoting the formation of a stable covalent thrombin–anti-thrombin complex. Only pentasaccharide-containing heparin chains composed of at least 18 saccharide units (which corresponds to a molecular weight of 5400) are of sufficient length to bridge thrombin and antithrombin together. With a mean molecular weight of 15,000, and a range of 5000 to 30,000, most of the chains of unfractionated heparin are long enough to produce this bridging. Consequently, by definition, heparin has equal capacity to promote the inhibition of thrombin and factor Xa by antithrombin and is assigned a 1:1 ratio of anti-factor Xa to anti-factor IIa (thrombin) activity.<sup>27</sup>

Heparin induces the release of tissue factor pathway inhibitor (TFPI), a factor Xa-dependent inhibitor of tissue factor-bound factor VIIa, from the endothelium.<sup>28</sup> TFPI may contribute to the antithrombotic activity of heparin. Longer heparin chains induce the release of more TFPI than shorter chains.<sup>28</sup>

### Pharmacology of Heparin

Heparin must be given parenterally. It is usually administered subcutaneously when given for prophylaxis and by continuous intravenous infusion when used for therapeutic purposes. If heparin is given subcutaneously for treatment of thrombosis, the dose of heparin must be high enough to overcome the limited bioavailability associated with this method of delivery.

In the circulation, heparin binds to the endothelium. Heparin binding to endothelial cells explains its dose-dependent clearance. At low doses, the half-life of heparin is short because it rapidly binds to the endothelium.<sup>27</sup> With higher doses of heparin, the endothelium is saturated and the half-life is longer.<sup>27</sup> Because of this phenomenon, the plasma half-life of heparin ranges from 30 to 60 minutes with bolus intravenous doses of 25 and 100 units/kg, respectively.<sup>27</sup> Clearance of heparin is mainly extrarenal; heparin binds to macrophages, which internalize and depolymerize the long heparin chains and secrete shorter chains back into the circulation.

Once the endothelium is saturated, heparin enters the circulation where it binds plasma proteins other than antithrombin, a phenomenon that reduces the anticoagulant activity of heparin. Some of the heparin-binding proteins in plasma are acute-phase reactants whose levels are elevated in ill patients.

Since the levels of heparin-binding proteins in plasma vary from person to person, the anticoagulant response to fixed or weight-adjusted doses of heparin is unpredictable. Consequently, coagulation monitoring is essential to ensure that a therapeutic response is obtained. This is particularly important when heparin is administered for treatment of established thrombosis because a subtherapeutic anticoagulant response renders patients at risk for recurrent thrombosis, whereas excessive anticoagulation increases the risk for bleeding.

The interaction of heparin with plasma proteins also contributes to the phenomenon of heparin rebound. Defined as the reappearance of anticoagulant activity after adequate neutralization of heparin with protamine, heparin rebound may contribute to excessive bleeding after cardiac surgery. This phenomenon likely reflects the slow release of protein-bound heparin after circulating heparin is neutralized by protamine.

**TABLE 41.1**

### Pharmacokinetic and Biophysical Limitations of Heparin

Limitations	Mechanism
Poor bioavailability at low doses	Limited absorption of long heparin chains
Dose-dependent clearance	Binds to endothelial cells
Variable anticoagulant response	Binds to plasma proteins whose levels vary from patient to patient
Reduced activity in the vicinity of platelet-rich thrombi	Neutralized by platelet factor 4 released from activated platelets
Limited activity against factor Xa incorporated in the prothrombinase complex and thrombin bound to fibrin	Reduced capacity of the heparin–antithrombin complex to inhibit factor Xa bound to activated platelets and thrombin bound to fibrin

Heparin rebound can be managed by administration of additional protamine by intravenous bolus or as a low-dose continuous infusion.<sup>29</sup>

### Monitoring the Anticoagulant Effect of Heparin

Heparin therapy can be monitored using the activated clotting time (ACT), activated partial thromboplastin time (aPTT) or anti-factor Xa level. The ACT, which is less sensitive than the aPTT and can be measured at the bedside, is used to monitor the high doses of heparin given during PCI or cardiac or vascular surgery. The aPTT is the test most often used to monitor therapeutic doses of heparin. If anti-factor Xa levels are measured, the therapeutic level ranges from 0.3 to 0.7 units/mL.

### Dosing

For prophylaxis, heparin is usually given in fixed doses of 5000 units subcutaneously two or three times daily. With these low doses, coagulation monitoring is unnecessary.<sup>30</sup> In contrast, monitoring is essential when the drug is given in therapeutic doses. Fixed-dose or weight-based heparin nomograms are used to standardize heparin dosing and to shorten the time required to achieve a therapeutic anticoagulant response.

### Limitations of Heparin

Heparin has pharmacokinetic and biophysical limitations (Table 41.1). The pharmacokinetic limitations reflect heparin's propensity to bind in a pentasaccharide-independent fashion to cells and plasma proteins. Heparin binding to endothelial cells explains its dose-dependent clearance, whereas binding to plasma proteins results in a variable anticoagulant response and can lead to heparin resistance.

### Side Effects

The most common side effect of heparin is bleeding. Other complications include thrombocytopenia, osteoporosis, and elevated levels of transaminases.

## Bleeding

The risk for heparin-induced bleeding increases with higher heparin doses. Concomitant administration of antiplatelet or fibrinolytic agents increases the risk for bleeding, as does recent surgery or trauma. Heparin-treated patients with serious bleeding can be given intravenous protamine sulfate to neutralize the heparin. Protamine sulfate, a mixture of basic polypeptides isolated from salmon sperm, binds heparin with high affinity, and the resultant protamine–heparin complexes are then cleared. Typically, 1 mg of protamine sulfate neutralizes 100 units of heparin. Anaphylactoid reactions to protamine sulfate<sup>31</sup> can occur, and drug administration by slow intravenous infusion is recommended to reduce the risk for these problems.<sup>31</sup>

## Thrombocytopenia

Heparin can cause thrombocytopenia. Heparin-induced thrombocytopenia (HIT) is an antibody-mediated process that is triggered by antibodies directed against neoantigens on PF4 that are exposed when heparin binds to this protein. These antibodies, which usually are of the IgG subtype, bind simultaneously to the heparin–PF4 complex and to platelet Fc receptors. Such binding activates the platelets and generates platelet microparticles. Circulating microparticles are prothrombotic because they express anionic phospholipids on their surface and can bind clotting factors, thereby promoting thrombin generation.

The clinical features of HIT are illustrated in Table 41.2. Typically, HIT occurs 5 to 14 days after initiation of heparin therapy, but it can manifest earlier if the patient has received heparin within the past 3 months.<sup>32</sup> Even a 50% decrease in the platelet count from the pretreatment value should raise the suspicion of HIT in those receiving heparin.<sup>33</sup> HIT is more common in surgical patients than in medical patients and, like many autoimmune disorders, occurs more frequently in females than in males.

HIT can be associated with thrombosis, either arterial or venous. Venous thrombosis, which manifests as deep vein thrombosis and/or pulmonary embolism, is more common than arterial thrombosis. Arterial thrombosis can manifest as ischemic stroke or acute MI. Rarely, platelet-rich thrombi in the distal aorta or iliac arteries can cause critical limb ischemia<sup>33</sup> (see Ch. 40, Disorders of Coagulation: Hypercoagulable States).

The diagnosis of HIT is established using enzyme-linked assays to detect antibodies against heparin–PF4 complexes or with platelet activation assays. Enzyme-linked assays are sensitive, but can be positive in the absence of any clinical evidence of HIT.<sup>33</sup> The most specific diagnostic test is the serotonin release assay. This test is performed by quantifying serotonin release when washed platelets loaded with labeled serotonin are exposed to patient serum in the absence or presence of varying concentrations of heparin. If the patient serum contains the HIT antibody, heparin addition induces platelet activation and subsequent serotonin release.<sup>33</sup>

Management of HIT is outlined in Table 41.3. Heparin should be stopped in patients with suspected or documented HIT, and an alternative anticoagulant should be administered

**TABLE 41.2**

### Features of Heparin-Induced Thrombocytopenia

Features	Details
Thrombocytopenia	Platelet count of 100,000/ $\mu$ L or less or a decrease in platelet count of 50% or more
Timing	Platelet count falls 5–10 days after starting heparin
Type of heparin	More common with unfractionated heparin than LMWH. Rare with fondaparinux.
Type of patient	More common in surgical patients than medical patients; more common in women than men
Thrombosis	Venous thrombosis more common than arterial thrombosis

**TABLE 41.3**

### Management of Heparin-induced Thrombocytopenia

Stop all heparin

Give an alternative anticoagulant, such as argatroban, bivalirudin, danaparoid, fondaparinux or rivaroxaban

Do not give platelet transfusions

Do not give warfarin until the platelet count returns to its baseline level. If warfarin was administered, give vitamin K to restore the INR to normal

Evaluate for thrombosis, particularly deep vein thrombosis

to prevent or treat thrombosis.<sup>34</sup> The agents most often used for this indication are parenteral direct thrombin inhibitors (such as argatroban or bivalirudin) or parenteral or oral factor Xa inhibitors (such as fondaparinux, danaparoid or rivaroxaban). The alternative anticoagulant should be continued until the platelet count is normal or the diagnosis of HIT is excluded. Warfarin should be avoided in HIT patients because it can trigger skin necrosis and thrombosis. These complications occur because warfarin lowers the levels of protein C and many HIT patients already have low levels of this anticoagulant protein because of increased thrombin generation.

## Low-Molecular-Weight Heparin

Consisting of smaller fragments of heparin, LMWH is prepared from unfractionated heparin by controlled enzymatic or chemical depolymerization. The mean molecular weight of LMWH is 5000, one-third the mean molecular weight of unfractionated heparin.<sup>35</sup> LMWH has advantages over heparin (Table 41.4) and has replaced heparin for most indications.

### Mechanism of Action

Like heparin, LMWH exerts its anticoagulant activity by activating antithrombin. With a mean molecular weight of 5000, which corresponds to about 17 saccharide units, at least half of the pentasaccharide-containing chains of LMWH are too

**TABLE 41.4** Advantages of LMWH Over Heparin

Advantage	Consequence
Better bioavailability and longer half-life after subcutaneous injection	Can be given subcutaneously once or twice daily for both prophylaxis and treatment
Dose-independent clearance	Simplified dosing
Predictable anticoagulant response	Coagulation monitoring is unnecessary in most patients
Lower risk of heparin-induced thrombocytopenia	Safer than heparin for short- or long-term administration
Lower risk of osteoporosis	Safer than heparin for extended administration

short to bridge thrombin to antithrombin (Fig. 41.2). However, these chains retain the capacity to accelerate factor Xa inhibition by antithrombin because this activity is largely the result of the conformational changes in antithrombin evoked by pentasaccharide binding. Consequently, LMWH catalyzes factor Xa inhibition more than thrombin inhibition.<sup>35</sup> Depending on their molecular weight distribution, the anti-factor Xa to anti-factor IIa ratios of the various LMWH preparations range from 2:1 to 9:1.<sup>36</sup>

### Pharmacology of LMWH

Although usually given subcutaneously, LMWH also can be administered intravenously if a rapid anticoagulant response is needed. LMWH has pharmacokinetic advantages over heparin.<sup>35</sup> These advantages reflect the fact that shorter heparin chains bind less avidly to endothelial cells, macrophages, and heparin-binding plasma proteins. Reduced binding to endothelial cells and macrophages eliminates the rapid, dose-dependent, and saturable mechanism of clearance characteristic of unfractionated heparin. Instead, the clearance of LMWH is dose independent and its plasma half-life is longer. Based on measurement of anti-factor Xa levels, LMWH has a plasma half-life of about 4–6 hours. LMWH is cleared almost exclusively by the kidneys, and the drug can accumulate in patients with renal insufficiency.<sup>35</sup>

LMWH exhibits about 90% bioavailability after subcutaneous injection.<sup>35</sup> Because LMWH binds less avidly to heparin-binding proteins in plasma than heparin, LMWH produces a more predictable dose response and resistance to LMWH is rare. With a longer half-life and more predictable anticoagulant response, LMWH can be given subcutaneously once or twice daily without coagulation monitoring.<sup>35</sup> These properties render LMWH more convenient than unfractionated heparin. Capitalizing on this feature, studies in patients with venous thromboembolism have shown that home treatment with LMWH is as effective and safe as in-hospital treatment with continuous intravenous infusions of heparin. Out-patient treatment with LMWH streamlines care, reduces healthcare costs, and increases patient satisfaction (see Ch. 148: Acute Lower Extremity Deep Venous Thrombosis: Presentation, Diagnosis, and Medical Treatment).

### LMWH Monitoring

In most patients, LMWH does not require coagulation monitoring. If monitoring is necessary, anti-factor Xa levels must be measured because LMWH has little effect on the aPTT. Therapeutic anti-factor Xa levels with LMWH range from 0.5 to 1.2 units/mL when measured 3 to 4 hours after drug administration. When LMWH is given in prophylactic doses, peak anti-factor Xa levels of 0.2 to 0.5 units/mL are desirable.<sup>37</sup>

Indications for LMWH monitoring include renal insufficiency and obesity. LMWH monitoring in patients with a creatinine clearance of 50 mL/min or less is advisable to ensure that there is no drug accumulation. Although weight-adjusted LMWH dosing appears to produce therapeutic anti-factor Xa levels in patients who are overweight, this approach has not been extensively evaluated in those with morbid obesity. It may be advisable to monitor the anticoagulant activity of LMWH during pregnancy because dose requirements can change, particularly in the third trimester.<sup>37</sup> Monitoring also should be considered in high-risk settings, such as in pregnant women with mechanical heart valves who are given LMWH for prevention of valve thrombosis.

### LMWH Dosing

The doses of LMWH recommended for prophylaxis or treatment vary depending on the LMWH preparation. For prophylaxis, once-daily subcutaneous doses of 4000 to 5000 units are often used, whereas doses of 2500 to 3000 units are given when the drug is administered twice daily. For treatment of venous thromboembolism, a dose of 150 to 200 units/kg is given if the drug is administered once daily. If a twice-daily regimen is employed, a dose of 100 units/kg is given. In patients with unstable angina, LMWH is given subcutaneously on a twice-daily basis at a dose of 100 to 120 units/kg.<sup>35</sup>

### Side Effects

The major complication of LMWH is bleeding. Meta-analyses have suggested that the risk for major bleeding may be lower with LMWH than with unfractionated heparin.<sup>38</sup> HIT and osteoporosis are less common with LMWH than with unfractionated heparin.<sup>35</sup>

### Bleeding

As with heparin, bleeding with LMWH is more common in patients receiving concomitant therapy with antiplatelet or fibrinolytic drugs. Recent surgery, trauma, or underlying hemostatic defects also increase the risk for bleeding with LMWH.<sup>39</sup>

Although protamine sulfate can be used as an antidote for LMWH, it incompletely neutralizes the anticoagulant activity of LMWH because protamine sulfate binds only the longer chains of LMWH.<sup>40</sup> Since longer chains are responsible for catalysis of thrombin inhibition by antithrombin, protamine sulfate completely reverses the anti-factor IIa activity of LMWH. In contrast, protamine sulfate only partially reverses the anti-factor Xa activity of LMWH because the shorter pentasaccharide-containing chains of LMWH do not bind to protamine sulfate. Consequently, patients at high risk for bleeding may be more safely treated with continuous intravenous unfractionated heparin than with subcutaneous LMWH.

**TABLE 41.5**

**Comparison of the features of Heparin, Low-Molecular-Weight Heparin, and Fondaparinux**

Features	Heparin	LMWH	Fondaparinux
Source	Biologic	Biologic	Synthetic
Molecular weight	15,000	5000	1500
Target	Xa and IIa	Xa and IIa	Xa
Bioavailability (%)	30	90	100
Half-life (h)	1	4	17
Renal excretion	No	Yes	Yes
Protamine reversal	Complete	Partial	No
HIT	<5%	<1%	Never

### Thrombocytopenia

The risk for HIT is about fivefold lower with LMWH than with heparin.<sup>41</sup> LMWH binds less avidly to platelets and causes less PF4 release. Furthermore, with lower affinity for PF4 than heparin, LMWH is less likely to induce the conformational changes in PF4 that trigger the formation of HIT antibodies.

LMWH should not be used to treat HIT patients<sup>34</sup> because most HIT antibodies exhibit cross-reactivity with LMWH. This *in vitro* cross-reactivity is not simply a laboratory phenomenon; cases of worsening thrombocytopenia and thrombosis have been reported when HIT patients are treated with LMWH.

### Fondaparinux

A synthetic analog of the antithrombin-binding pentasaccharide sequence, fondaparinux differs from LMWH in several ways (Table 41.5). Fondaparinux is licensed for thromboprophylaxis in general surgical and high-risk orthopedic patients and as an alternative to heparin or LMWH for initial treatment of patients with established venous thromboembolism. Although approved as an alternative to heparin or LMWH in patients with acute coronary syndrome in Europe and Canada, fondaparinux is not licensed for this indication in the United States.

#### Mechanism of Action

As a synthetic analog of the antithrombin-binding pentasaccharide sequence found in heparin and LMWH, fondaparinux has a molecular weight of 1728. Fondaparinux binds only to antithrombin (see Fig. 41.2) and is too short to bridge thrombin to antithrombin. Consequently, fondaparinux catalyzes factor Xa inhibition by antithrombin and does not enhance the rate of thrombin inhibition.<sup>42</sup>

#### Pharmacology of Fondaparinux

Fondaparinux exhibits complete bioavailability after subcutaneous injection. With no binding to endothelial cells or plasma proteins, the clearance of fondaparinux is dose independent and its plasma half-life is 17 hours.<sup>43</sup> The drug is given

subcutaneously once daily. Because fondaparinux is cleared unchanged via the kidneys, it is contraindicated in patients with a creatinine clearance less than 30 mL/min and it should be used with caution in those with a creatinine clearance less than 50 mL/min.<sup>42,43</sup>

Fondaparinux produces a predictable anticoagulant response after administration in fixed doses because it does not bind to plasma proteins. The drug is given at a dose of 2.5 mg once daily for prevention of venous thromboembolism. For initial treatment of established venous thromboembolism, fondaparinux is given at a dose of 7.5 mg once daily. The dose can be reduced to 5 mg once daily for those weighing less than 50 kg and increased to 10 mg once daily for those over 100 kg. When given in these doses, fondaparinux is as effective as heparin or LMWH for initial treatment of patients with deep vein thrombosis or pulmonary embolism and produces similar rates of bleeding.<sup>44</sup>

#### Side Effects

Although fondaparinux can induce the formation of HIT antibodies, HIT is rare with fondaparinux. In contrast to LMWH, there is no cross-reactivity of fondaparinux with HIT antibodies. Consequently, fondaparinux appears to be effective for treatment of HIT patients,<sup>45</sup> although large clinical trials supporting its use in this setting are lacking.

The major side effect of fondaparinux is bleeding. There is no antidote for fondaparinux. Protamine sulfate has no effect on the anticoagulant activity of fondaparinux because it fails to bind to the drug. Recombinant activated factor VII reverses the anticoagulant effects of fondaparinux in volunteers, but it is unknown whether this agent controls fondaparinux-induced bleeding.

## PARENTERAL DIRECT THROMBIN INHIBITORS

Heparin and LMWH are indirect inhibitors of thrombin because their activity is mediated by antithrombin. In contrast, direct thrombin inhibitors do not require a plasma cofactor; instead, these agents bind directly to thrombin and block its interaction with its substrates. Parenteral direct thrombin inhibitors include lepirudin and desirudin – recombinant forms of hirudin – as well as argatroban, and bivalirudin (Table 41.6). Lepirudin and desirudin are no longer available. Argatroban is licensed for treatment of patients with HIT and bivalirudin is approved as an alternative to heparin in patients undergoing percutaneous coronary interventions, including those with HIT.<sup>46</sup>

#### Argatroban

A univalent inhibitor that targets the active site of thrombin, argatroban is metabolized in the liver.<sup>46</sup> Consequently, this drug must be used with caution in patients with hepatic insufficiency. Argatroban is not cleared via the kidneys so this drug may be safer than fondaparinux for HIT patients with renal insufficiency.

**TABLE 41.6**

## Comparison of the Properties of Hirudin, Bivalirudin, and Argatroban

	Hirudin	Bivalirudin	Argatroban
Molecular mass (Da)	7000	1980	527
Site(s) of interaction with thrombin	Active site and exosite 1	Active site and exosite 1	Active site
Renal clearance	Yes	No	No
Hepatic metabolism	No	No	Yes
Plasma half-life (min)	60	25	45

Argatroban is administered by continuous intravenous infusion and has a plasma half-life of about 45 minutes. The aPTT is used to monitor its anticoagulant effect, and the dose is adjusted to achieve an aPTT 1.5 to 3 times the baseline value, but not to exceed 100 seconds. Argatroban also prolongs the international normalized ratio (INR), a feature that can complicate the transitioning of patients to warfarin. This problem can be circumvented by using the levels of factor X to monitor warfarin in place of the INR. Alternatively, argatroban can be stopped for 2 to 3 hours before INR determination.

### Bivalirudin

A synthetic 20-amino acid analog of hirudin, bivalirudin is a divalent thrombin inhibitor.<sup>46</sup> Thus the NH<sub>2</sub>-terminal portion of bivalirudin interacts with the active site of thrombin, whereas its COOH-terminal tail binds to exosite 1, the substrate-binding domain on thrombin. Bivalirudin has a plasma half-life of 25 min, the shortest half-life of all the parenteral direct thrombin inhibitors.<sup>46</sup> Bivalirudin is degraded by peptidases and is partially excreted via the kidneys. When given in high doses in the cardiac catheterization laboratory, the anticoagulant activity of bivalirudin is monitored using the activated clotting time. With lower doses, its activity can be assessed using the aPTT.

Studies comparing bivalirudin with heparin suggested that bivalirudin produced less bleeding.<sup>47</sup> This feature plus its short half-life prompted the use of bivalirudin as an alternative to heparin in patients undergoing PCI.<sup>48</sup> Bivalirudin also has been used successfully in HIT patients who require PCIs.<sup>49</sup>

## ORAL ANTICOAGULANTS

Current oral anticoagulant practice dates back almost 60 years to when the vitamin K antagonists (VKAs) such as warfarin were discovered during investigation into the cause of hemorrhagic disease in cattle. Over the past decade, however, direct oral anticoagulants (DOACs) have replaced warfarin for many indications. The DOACs include dabigatran, which inhibits thrombin, and rivaroxaban, apixaban, and edoxaban, which inhibit factor Xa.

### Warfarin

A water-soluble vitamin K antagonist initially developed as a rodenticide; warfarin is the coumarin derivative most often prescribed in North America. Like other VKAs, warfarin interferes with the synthesis of the vitamin K-dependent clotting proteins, which include prothrombin (factor II) and factors VII, IX, and X. VKAs also reduce the synthesis of the vitamin K-dependent anticoagulant proteins, proteins C, S and Z.

### Mechanism of Action

Warfarin inhibits vitamin K epoxide reductase (VKOR), thereby blocking the  $\gamma$ -carboxylation process. This results in the synthesis of vitamin K-dependent clotting proteins that are only partially  $\gamma$ -carboxylated. Warfarin acts as an anticoagulant because these partially  $\gamma$ -carboxylated proteins have reduced or absent biologic activity. The onset of action of warfarin is delayed until the newly synthesized clotting factors with reduced activity gradually replace their fully active counterparts.

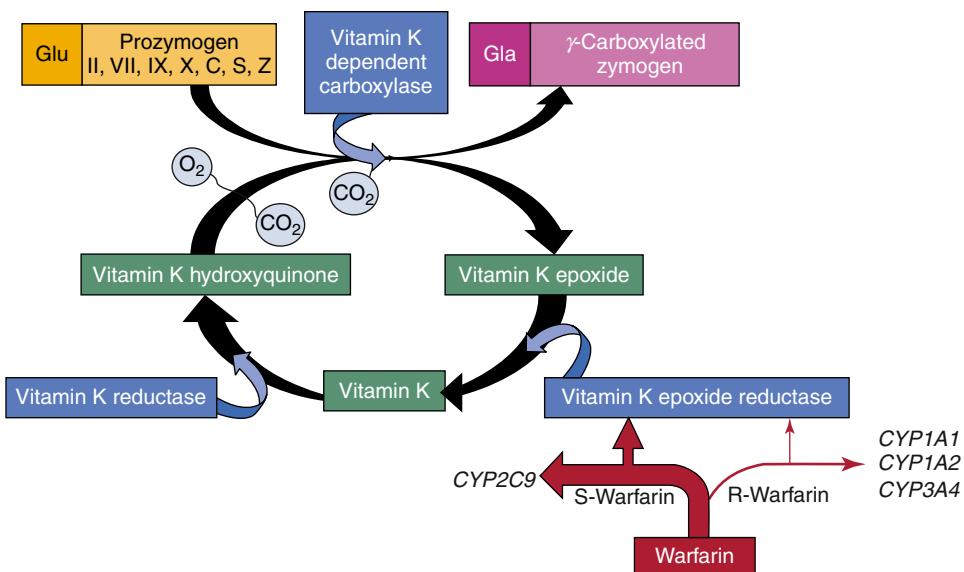
The antithrombotic effect of warfarin depends on a reduction in the functional levels of factor X and prothrombin, clotting factors that have half-lives of 24 and 72 hours, respectively.<sup>50</sup> Because of the delay in achieving an antithrombotic effect, initial treatment with warfarin is supplemented by concomitant administration of a rapidly acting parenteral anticoagulant, such as heparin, LMWH or fondaparinux, in patients with established thrombosis, or at high risk for thrombosis.<sup>50</sup>

### Pharmacology

Warfarin is a racemic mixture of *R*- and *S*-isomers. Warfarin is rapidly and almost completely absorbed from the gastrointestinal tract. Levels of warfarin in the blood peak about 90 minutes after drug administration.<sup>50</sup> Racemic warfarin has a plasma half-life of 36 to 42 hours, and more than 97% of circulating warfarin is bound to albumin. Only the small fraction of unbound warfarin is biologically active.<sup>50</sup>

Warfarin accumulates in the liver, where the two isomers are metabolized via distinct pathways. Oxidative metabolism of the more active *S*-isomer is mediated by CYP2C9 (Fig. 41.3). Two relatively common variants, CYP2C9\*2 and CYP2C9\*3 have reduced activity. Patients with these variants require lower maintenance dose of warfarin. Polymorphisms in the C1 subunit of vitamin K reductase (VKORC1) also can influence the anticoagulant response to warfarin.<sup>51,52</sup> These findings have prompted the recommendation that patients starting on warfarin be tested for these polymorphisms and that this information be incorporated into their warfarin dosing algorithms. However, it remains uncertain as to whether warfarin dosing algorithms that incorporate pharmacogenetics data improve clinical outcomes.

In addition to genetic factors, the anticoagulant effect of warfarin is influenced by diet, drugs, and various disease states. Fluctuations in dietary vitamin K intake affect the activity of warfarin. A wide variety of drugs can alter absorption, clearance, or metabolism of warfarin.<sup>50</sup> Because of the variability in the anticoagulant response to warfarin, coagulation monitoring is essential to ensure that a therapeutic response is obtained.



**Figure 41.3** The Vitamin K Cycle and its Inhibition by Warfarin. Dietary vitamin K is reduced by vitamin K reductase to generate vitamin K hydroquinone. Vitamin K hydroquinone serves as a cofactor for the vitamin K-dependent carboxylase that converts glutamic acid residues at the N-termini of the vitamin K-dependent precursors to  $\gamma$ -carboxyglutamic acid residues, thereby creating the so-called Gla-domain. By binding calcium, the Gla-domain is critical for the interaction of the vitamin K-dependent clotting factors with negatively charged phospholipid membranes. During vitamin K-dependent carboxylation, vitamin K is oxidized to vitamin K epoxide. Vitamin K epoxide is then converted to vitamin K by vitamin K epoxide reductase. Vitamin K antagonists, such as warfarin, interfere with this cycle by inhibiting vitamin K epoxide reductase and vitamin K reductase. Of these two enzymes, vitamin K antagonists more readily block vitamin K epoxide reductase than vitamin K reductase. Consequently, supplemental vitamin K can overcome the inhibitory effects of vitamin K antagonists.

## Monitoring

Warfarin therapy is most often monitored using the prothrombin time, a test that is sensitive to reductions in the levels of prothrombin, factor VII and factor X. The test is performed by adding thromboplastin, a reagent that contains tissue factor, phospholipid, and calcium, to citrated plasma and determining the time to clot formation. The INR was developed to overcome the varying sensitivity of thromboplastin reagents to reductions in the levels of the vitamin K-dependent clotting factors.

For most indications, warfarin is administered in doses that produce a target INR of 2.0 to 3.0. An exception is patients with mechanical heart valves in the mitral position or in patients with mechanical heart valves who also have atrial fibrillation, where a target INR of 2.5 to 3.5 is recommended.<sup>50</sup> Studies in atrial fibrillation demonstrate an increased risk for cardioembolic stroke when the INR falls below 1.7 and an increase in bleeding with INR values over 4.5.<sup>53</sup> These findings highlight the fact that vitamin K antagonists have a narrow therapeutic window.

## Dosing

Warfarin is usually started at a dose of 5 to 10 mg. The dose is then titrated to achieve the desired target INR. Because of its delayed onset of action, patients with established thrombosis or those at high risk for thrombosis are given concomitant treatment with a rapidly acting parenteral anticoagulant, such as heparin, LMWH, or fondaparinux. Initial prolongation of the INR reflects reduction in the functional levels of factor VII.

Consequently, concomitant treatment with the parenteral anticoagulant should be continued until the INR has been therapeutic for at least 2 consecutive days. A minimum 5-day course of parenteral anticoagulation is recommended to ensure that the levels of prothrombin have been reduced into the therapeutic range with warfarin.<sup>50</sup>

Because warfarin has a narrow therapeutic window, frequent coagulation monitoring is essential to ensure that a therapeutic anticoagulant response is obtained. Even patients with stable warfarin dose requirements should have their INR determined every 4 weeks. More frequent monitoring is necessary when new medications are introduced because so many drugs enhance or reduce the anticoagulant effects of warfarin.

## Side Effects

Like all anticoagulants, the major side effect of warfarin is bleeding. A rare complication is skin necrosis. Warfarin crosses the placenta and can cause fetal abnormalities. Consequently, warfarin should not be used during pregnancy.

### Skin necrosis

A rare complication of warfarin, skin necrosis usually is seen 2 to 5 days after initiation of therapy. Well-demarcated erythematous lesions form on the thighs, buttocks, breasts, or toes. Typically, the center of the lesion becomes progressively necrotic. Examination of skin biopsies taken from the border of these lesions reveals thrombi in the microvasculature.

Warfarin-induced skin necrosis is seen in patients with congenital or acquired deficiencies of protein C or protein

**TABLE 41.7** Pharmacological Properties of the Direct Oral Anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Thrombin (IIa)	Factor Xa	Factor Xa	Factor Xa
Active drug	No	Yes	Yes	Yes
Onset time (h)	0.5–2	2–4	3–4	1–3
Half-life (h)	12–17	5–13	~12	9–11
Renal excretion (%)	80	33	27	50
CYP metabolism	No	Yes	Yes	Limited
P-glycoprotein substrate	Yes	Yes	Yes	Yes
Reversal agent	Idarucizumab	Andexanet	Andexanet	Andexanet

S. Initiation of warfarin therapy in these patients produces a precipitous fall in plasma levels of proteins C or S, thereby eliminating this important anticoagulant pathway before warfarin exerts an antithrombotic effect through lowering of the functional levels of factor X and prothrombin. The resultant procoagulant state triggers thrombosis. Why the thrombosis is localized to the microvasculature of fatty tissues is unclear.

Treatment involves discontinuation of warfarin and, if needed, reversal with vitamin K. An alternative anticoagulant, such as heparin or LMWH, should be given in patients with thrombosis. Protein C concentrates can be given to protein C-deficient patients to accelerate healing of the skin lesions; fresh frozen plasma may be of value for those with protein S deficiency. Occasionally, when there is extensive skin loss, grafting is necessary.

Because of the potential for skin necrosis, patients with known protein C or protein S deficiency require overlapping treatment with a parenteral anticoagulant when initiating warfarin therapy. Warfarin should be started in low doses in these patients, and the parenteral anticoagulant should be continued until the INR is therapeutic for at least 2 to 3 consecutive days. Alternatively, a DOAC could be used in place of warfarin but data with these agents in patients with severe protein C or protein S deficiency are lacking.

### Pregnancy

Warfarin crosses the placenta and can cause fetal abnormalities or bleeding. The fetal abnormalities include a characteristic embryopathy, which consists of nasal hypoplasia and stippled epiphyses. The risk for embryopathy is highest if warfarin is given in the first trimester of pregnancy.<sup>54</sup> Central nervous system abnormalities also can occur with exposure to coumarin drugs at any time during pregnancy. Finally, maternal administration of warfarin produces an anticoagulant effect in the fetus that can cause bleeding. This is of particular concern at delivery when trauma to the head during passage through the birth canal can lead to intracranial bleeding. Because of these potential problems, warfarin is contraindicated in pregnancy, particularly in the first and third trimesters. Instead, heparin, LMWH, or fondaparinux can be given during pregnancy for prevention or treatment of thrombosis.

Warfarin does not pass into the breast milk. Consequently, warfarin can safely be given to nursing mothers.

### Direct Oral Anticoagulants

DOACs have a rapid onset of action and have half-lives that permit once- or twice-daily administration (Table 41.7). Designed to produce a predictable level of anticoagulation, the DOACs are more convenient than warfarin because they can be given in fixed doses without routine coagulation monitoring.

### Mechanism of Action

DOACs are small molecules that bind reversibly to the active site of their target enzyme. Dabigatran inhibits thrombin, whereas apixaban, edoxaban, and rivaroxaban inhibit factor Xa. Table 41.7 summarizes the pharmacologic features of these agents.

### Indications and Dosing

All four DOACs are licensed for stroke prevention in patients with non-valvular atrial fibrillation, which encompasses patients without mechanical heart valves or severe rheumatic mitral valve disease, and for treatment of venous thromboembolism (VTE). Dabigatran, rivaroxaban and apixaban are licensed for thromboprophylaxis after elective hip or knee arthroplasty; edoxaban is only licensed for this indication in Japan. Finally, low-dose rivaroxaban is licensed for use with aspirin for secondary prevention in patients with coronary or peripheral artery disease. At doses of 15 or 20 mg once daily, rivaroxaban must be administered with food to enhance absorption. Apixaban and edoxaban can be given with or without food. Administration of dabigatran with food may reduce dyspepsia.

For secondary prevention of adverse cardiac or limb events in patients with coronary or peripheral artery disease, rivaroxaban is given at a dose of 2.5 mg twice daily on top of aspirin (81 or 100 mg once daily).

### Monitoring

Although administered without routine monitoring, determination of DOAC levels can be helpful in some cases, including assessment of adherence, detection of accumulation or overdose, identification of bleeding mechanisms, and determination of activity before surgery, intervention or reversal. For qualitative assessment of anticoagulant activity, the prothrombin time can be used for rivaroxaban and edoxaban and the aPTT for dabigatran. Because apixaban has such a limited

effect on the prothrombin time, anti-factor Xa assays are needed to assess its activity.<sup>55</sup> The effect of the drugs on tests of coagulation varies depending on the reagents used to perform the tests, and variability increases with conversion of the prothrombin time to an INR. Chromogenic anti-factor Xa assays and the diluted thrombin clotting time or ecarin clotting with appropriate calibrators provide quantitative assays to measure plasma levels of the factor Xa inhibitors and dabigatran, respectively.<sup>55</sup> In patients requiring urgent surgery, bleeding is unlikely with DOAC levels less than 30 ng/mL and reversal is unlikely to be necessary with levels less than 50 ng/mL.

### Side Effects

As with all anticoagulants, bleeding is the most common side effect of the DOACs. Although the DOACs are associated with less intracranial bleeding than warfarin, the risk for gastrointestinal bleeding is higher with dabigatran (at the 150-mg, twice-daily dose), rivaroxaban, and edoxaban (at the 60-mg once-daily dose) than with warfarin. Dyspepsia occurs in up to 10% of patients treated with dabigatran; this problem improves with time and can be minimized by taking the drug with food.

As small molecules, the DOACs pass through the placenta. Consequently, these agents are contraindicated in pregnancy, and when used by women of childbearing potential, appropriate contraception is important. Small amounts of rivaroxaban pass into breast milk, and it is unknown whether the other DOACs also do so. Therefore, DOACs should not be used in nursing mothers.

## Management of Bleeding with Oral Anticoagulants

### Warfarin

At least half of the bleeding complications with warfarin occur when the INR exceeds the therapeutic range. Patients with serious bleeding should be given vitamin K to reverse the warfarin (10 mg by slow intravenous infusion) and four-factor prothrombin complex concentrate (PCC) should be administered to replenish the missing clotting factors. Additional vitamin K should be given until the INR is in the normal range. PCC normalizes the INR more rapidly than fresh frozen plasma and is associated with a lower risk of heart failure and transfusion-related lung injury because the required volume is much less. Recombinant factor VIIa should not be used for warfarin reversal because it only supplements one of the missing factors.<sup>56,57</sup>

### DOACs

With minor bleeding, withholding one or two doses of drug is usually sufficient (Fig. 41.4). With more serious bleeding, the approach is like that with warfarin, except that vitamin K administration is of no benefit; the anticoagulant and any antiplatelet drugs should be withheld, the patient should be resuscitated with fluids and blood products as necessary, and the bleeding site should be identified and managed. Coagulation testing or measurement of DOAC level will determine

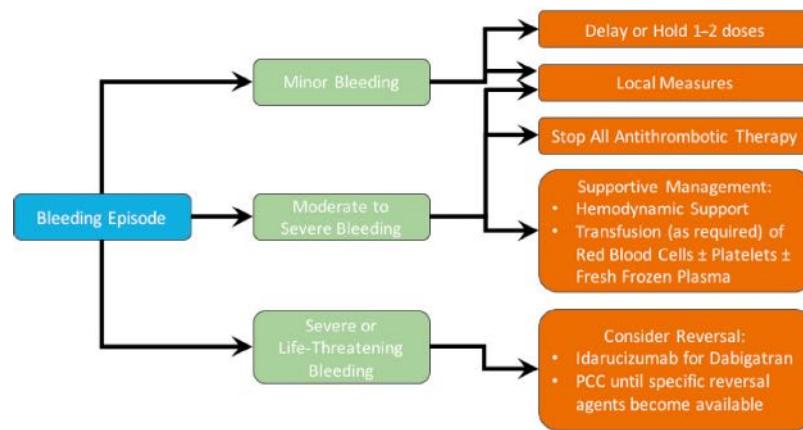
the extent of anticoagulation, and renal function should be assessed so that the half-life of the drug can be calculated. Timing of the last dose of anticoagulant is important, and oral activated charcoal may help prevent absorption of drug administered in the past 4 hours particularly in cases of overdose. If bleeding continues or is life-threatening or if it occurs in a critical organ (e.g., intracranial) or in a closed space (e.g., the pericardium or retroperitoneum), reversal of the anticoagulant should be considered (Fig. 41.4).

Idarucizumab is licensed for dabigatran reversal in patients with serious bleeding or in those requiring urgent surgery or intervention.<sup>58</sup> A humanized antibody fragment, idarucizumab binds dabigatran with high affinity to form an essentially irreversible complex that is cleared by the kidneys. Idarucizumab is given intravenously as a 5-g bolus. Idarucizumab rapidly reverses the anticoagulant effects of dabigatran and normalizes the aPTT, diluted thrombin time, or ecarin clot time.<sup>59</sup>

Andexanet alfa is available for reversal of rivaroxaban, apixaban, and edoxaban. A recombinant variant of factor Xa without catalytic activity, andexanet serves as a decoy to sequester oral factor Xa inhibitors until they are cleared from the circulation.<sup>58</sup> Low- or high-dose intravenous andexanet regimens are used. The low-dose regimen starts with a bolus of 400 mg followed by an infusion of 4 mg/min for up to 120 min, whereas the high dose regimen starts with a bolus of 800 mg followed by an infusion of 8 mg/min for up to 120 min. The low-dose regimen is used for reversal of doses of rivaroxaban or apixaban of 10 mg or 5 mg or less, respectively, or for any dose of rivaroxaban or apixaban if the last dose was taken more than 8 hours prior to presentation. The high-dose regimen is used to reverse rivaroxaban or apixaban doses over 10 and 5 mg, respectively, if the last dose was taken less than 8 hours since presentation, or for reversal if the dose of rivaroxaban or apixaban or the timing of the last dose is unknown.

Andexanet alfa is expensive and is not available in all hospitals. Because of its cost, andexanet alfa is often reserved for reversal in patients with intracranial bleeds or for bleeds into a closed space such as retroperitoneal or pericardial bleeds. If andexanet is unavailable, the results of prospective cohort studies suggest that 4-factor PCC (25 to 50 units/kg) also is effective at restoring hemostasis.<sup>58</sup> If there is continued bleeding, activated PCC (50 units/kg) or recombinant factor VIIa (90 µg/kg) can be considered.<sup>58</sup>

Neither andexanet alfa nor PCC has been evaluated for reversal in patients requiring urgent surgery or intervention. Furthermore, andexanet alfa not only reverses oral factor Xa inhibitors but also reverses heparin and LMWH. This could be problematic in patients who require cardiac surgery or vascular surgery, procedures where heparin is used routinely. To circumvent this problem, most surgical procedures and interventions can be done without reversal and PCC can be given if necessary. For patients requiring surgery to stop bleeding such as those with a ruptured aortic aneurysm or with bleeding secondary to polytrauma, up front PCC administration can be considered.



**Figure 41.4** Flow diagram for the management of bleeding in patients taking DOACs.

## PERIOPERATIVE MANAGEMENT OF ANTICOAGULANT AGENTS

Warfarin should be stopped 5 days before surgery or invasive procedures to allow the INR to return to normal levels. The INR should be determined before surgery to ensure that it is less than 1.5. Recent studies indicate that bridging with low-molecular-weight heparin before and soon after surgery does not reduce the risk of thrombotic complications in most patients with atrial fibrillation and increases the risk of bleeding after surgery.<sup>60</sup> However, bridging is still indicated for patients at high risk for stroke or those with mechanical heart valves. Bridging can be done with intravenous heparin or with once- or twice-daily subcutaneous injections of LMWH when the INR falls below 2.0. Intravenous heparin should be stopped 4 to 6 hours before surgery, whereas the last dose of LMWH should be given 24 hours before surgery. Warfarin can be restarted 12 to 24 hours after surgery and patients should receive prophylactic doses of heparin or low-molecular-weight heparin after surgery until the INR is at least over 1.8. In the case of urgent surgery, warfarin can be rapidly reversed with PCC and intravenous vitamin K.

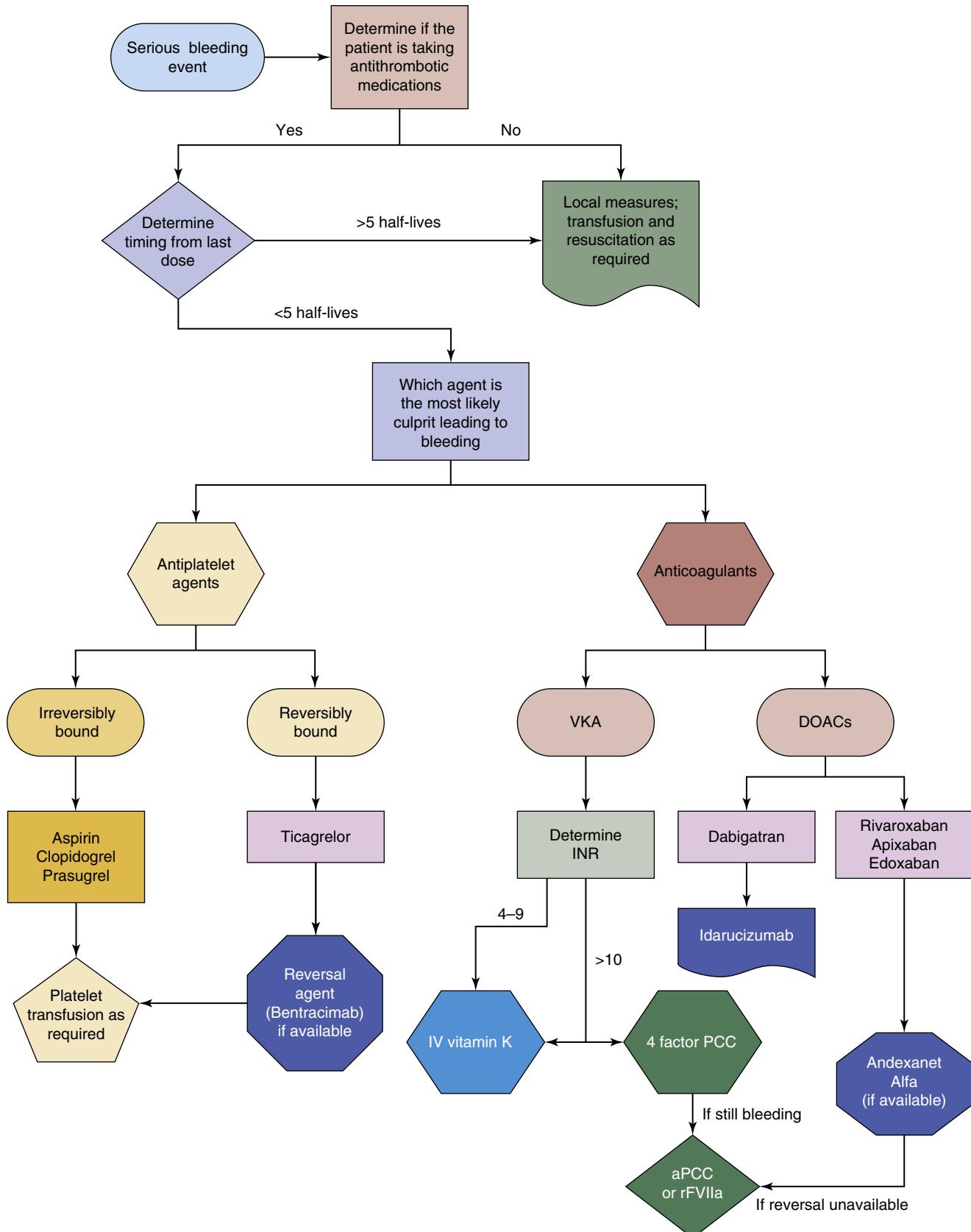
DOACs should be withheld for at least 1 day prior to procedures associated with a moderate risk of bleeding and for at least 2 days before procedures associated with a high risk of bleeding or longer if renal function is impaired. After surgery, patients should receive thromboprophylaxis with LMWH until hemostasis is restored, at which point DOACs can be restarted.

Cardiac procedures such as atrial fibrillation ablation or pacemaker implantation can safely be performed without interruption of the direct oral anticoagulants. However, it may be prudent to hold the dose in the morning of the day of the procedure to avoid intervention at peak drug levels.

## FUTURE DIRECTIONS

A better understanding of the biochemistry of blood coagulation and advances in structure-based drug design have resulted in the development of novel anticoagulant drugs. Based on the results of well-designed clinical trials, the choice of agents has expanded, and treatment has become more streamlined. Despite these advances, however, arterial and venous thromboembolic disorders remain a major cause of morbidity and mortality. Consequently, the search for better targets and more potent, safer, or more convenient antiplatelet and anticoagulant drugs continues.

## CHAPTER ALGORITHM



Diagnostic and Therapeutic Algorithm: Bleeding.

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# Antiplatelet Agents

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## INTRODUCTION

Platelets are the smallest blood cells in the human body, normally numbering  $150\text{--}350 \times 10^9/\text{L}$ , and play a central role in the normal homeostatic process of hemostasis and thrombosis. As first described in the 18th century,<sup>1</sup> platelets are involved in nearly all aspects of vascular occlusive disease. This includes the disruption of platelet- and fibrin-rich atherosclerotic plaques, which lead to further platelet aggregation and deposition causing thrombus formation and, possibly, clinically relevant thrombotic events.<sup>2</sup> Antiplatelet agents modulate the role of platelets in these delicate processes. Thus a detailed understanding of platelet function and antiplatelet pharmacology is essential for the practicing vascular specialist.

## NORMAL PLATELET FUNCTION AND PLATELET ACTIVATION

Normally platelets circulate without interacting with the blood vessel wall. This delicate balance is modulated by the interaction of platelets with the endothelium. The endothelium releases nitric oxide and prostacyclin to prevent platelet aggregation. In addition, endothelial cells express ADPase, which degrades adenosine diphosphate (ADP) released from activated platelets, further inhibiting platelet aggregation. A platelet life span ranges from 8 to 10 days.

Platelets are the essential components of primary hemostasis. Primary hemostasis is defined as the early stages of hemostasis to prevent blood loss. When vessel injury occurs, the subendothelium is exposed. Exposed tissue factor, subendothelial collagen, von Willebrand factor, and fibronectin interact with molecules expressed on the platelet surface ( $\alpha 2\beta 1$ , *glycoprotein Ib/IX*, and  $\alpha 5\beta 1$ ). These interactions induce a conformational change in platelet morphology and stimulate platelet granule release of ADP and thromboxane A2. Exposure of ADP receptors on activated platelets induces platelet aggregation by cross-linking ADP molecules. Thromboxane A2 induces vasoconstriction and further recruitment of platelets to the site of injury. Platelet activation also results in the expression of *glycoprotein IIb/IIIa (GP-IIb/IIIa)* on the platelet surface. *GP-IIb/IIIa* ligates divalent fibrinogen to bridge platelets, thus promoting aggregation. The platelet aggregates are woven into a fibrin mesh formed by the cleavage of fibrinogen by thrombin. This platelet plug forms the basis for the later stages of hemostasis. Antiplatelet agents modulate various steps in these intricate processes (Fig. 42.1).<sup>3-5</sup>

## THROMBOXANE INHIBITORS

### Aspirin

#### Mechanism of Action

Aspirin is the most commonly used antiplatelet agent. It is a nonselective, irreversible cyclooxygenase enzyme (*COX*) inhibitor. It irreversibly acetylates *COX-1*, interrupting the production of prostaglandin H2 and the production of thromboxane

A2 (TXA2) to prevent platelet aggregation.<sup>6,7</sup> At higher doses, *COX-2* is also inhibited, promoting the anti-inflammatory effect of aspirin.<sup>8</sup>

#### Indications and Dose

Aspirin is indicated for the prevention of cardiovascular events in patients with established coronary disease, peripheral arterial occlusive disease, or cerebrovascular occlusive disease.<sup>9</sup> More recently, the use of aspirin for primary prevention in patients without an established cardiovascular risk profile has been scrutinized,<sup>10</sup> but there is no consensus recommendation regarding aspirin use for primary prevention of adverse cardiovascular events.<sup>11,12</sup>

Aspirin doses range from 75 to 325 mg/daily. Non-enteric-coated aspirin can achieve platelet inhibition approximately 1 hour after ingestion. Enteric-coated aspirin may achieve platelet inhibition at 3 to 4 hours after ingestion.<sup>13</sup> Chewing aspirin can result in inhibition as rapidly as 20 minutes after ingestion and is independent of the enteric coating of the pill.<sup>14</sup>

#### Side-Effect Profile

The most common side effects involve the gastrointestinal (GI) tract and range from dyspepsia to gastritis and ulcers, which may lead to bleeding and/or perforation. *Helicobacter pylori* infection may predispose to a higher risk of GI bleed. The risk of bleeding is estimated to be between 1% and 3% per year and increases with the addition of other antiplatelet agents (e.g., clopidogrel) or anticoagulants (e.g., warfarin).<sup>13</sup>

Allergy to aspirin is a rare phenomenon (~0.3% of patients). Bronchospasm can occur in patients allergic to aspirin, and this stands as a contraindication to aspirin administration. Allergy to aspirin may be more common in patients with asthma, urticaria, nasal polyps, or chronic rhinitis and thus administration should be undertaken with caution.<sup>15</sup>

#### Perioperative Management

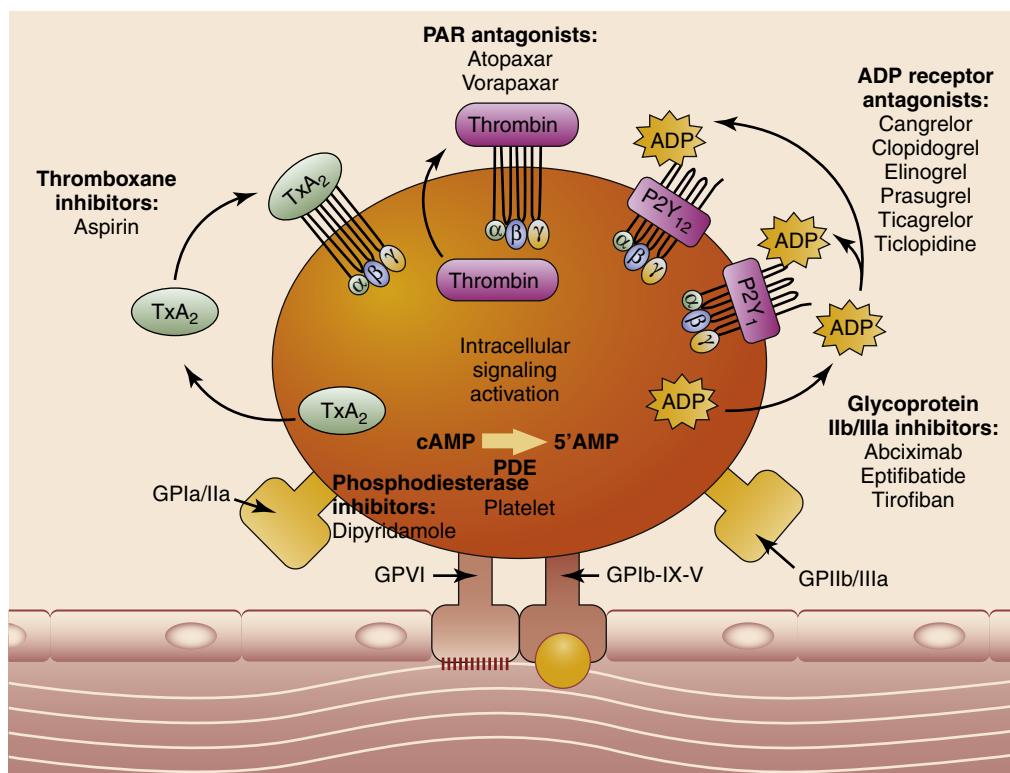
Aspirin may be discontinued 7 to 10 days before surgery in those at moderate to high risk for bleeding and a low estimated risk for cardiovascular events while off the medication. Otherwise, aspirin can be continued perioperatively in patients undergoing diagnostic or therapeutic interventions at low risk for bleeding. In patients undergoing vascular surgery, aspirin can be safely continued in the perioperative period.<sup>16,17</sup> In cases such as carotid interventions, aspirin should be initiated preoperatively in patients not already on antiplatelet therapy.

## THIENOPYRIDINES (ADENOSINE DIPHOSPHATE RECEPTOR ANTAGONISTS)

### Clopidogrel

#### Mechanism of Action

Clopidogrel is a prodrug that is activated by the hepatic cytochrome-450 (*CYP450*) enzyme system (mainly *CYP2C19*). It irreversibly inhibits *P2Y12* (a key ADP receptor) on the



**Figure 42.1** Platelet function and molecular targets of antiplatelet agents.<sup>5</sup> ADP, adenosine diphosphate; cAMP, cyclic adenosine monophosphate;  $TxA_2$ , thromboxane  $A_2$ ; PAR, protease-activated receptor.

platelet surface.<sup>18</sup> Because it requires activation, the onset to therapeutic inhibition can be variable and can be influenced by genetic polymorphisms of the *CYP450* system.<sup>19</sup>

### Indications and Dose

Clopidogrel is indicated for use in patients with unstable angina/non-ST-elevated myocardial infarction (UA/NSTEMI), ST-segment myocardial infarction (STEMI), recent myocardial infarction, recent cerebrovascular accident (CVA), or established peripheral arterial occlusive disease. Off-label use includes adjunctive therapy after percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) surgery, or peripheral artery percutaneous transluminal angioplasty. For patients with symptomatic carotid artery stenosis or with aspirin intolerance, clopidogrel is frequently used.

The usual daily dose of clopidogrel is 75 mg.<sup>20</sup> The time to platelet inhibition (the onset of action) is dose-dependent and may take to the second day of therapy to detect activity at the usual daily dose. During periods that require more rapid therapeutic levels (e.g., coronary stenting), a bolus dose between 300 and 600 mg of clopidogrel may be administered. This provides a more rapid onset of platelet inhibition (typically about 2 hours).<sup>21,22</sup>

### Side-Effect Profile

The main side effect of clopidogrel is bleeding, and this can occur at any site. The incidence of severe GI hemorrhage is estimated to be 2%.<sup>23</sup> Other, less common side effects include pruritus and epistaxis.<sup>23</sup>

### Perioperative Management

Clopidogrel should be discontinued 7 to 10 days prior to surgery (minimum of 5 days) before elective surgery, except in patients with coronary stents who have not completed a full course of dual antiplatelet therapy.

### Drug-Drug Interactions

Clopidogrel's antiplatelet effect may be influenced by other drugs metabolized via the *CYP450* enzyme system.<sup>24</sup> Specifically, proton-pump inhibitors, which are inhibitors of *CYP2C19*, may lessen the ability of clopidogrel to inhibit platelet aggregation. This interaction may not be clinically relevant for most patients; however, current recommendations are to avoid the administration of *CYP2C19* inhibitors concomitantly with clopidogrel, whenever possible.<sup>25</sup>

### Clopidogrel Resistance

The most important *CYP450* isoenzyme involved in clopidogrel metabolism (and thus activation) is *CYP2C19*. Patients with certain variant *CYP2C19* alleles (*CYP2C19\*2* or *CYP2C19\*3*) may have reduced conversion of clopidogrel to the active metabolite compared with wild-type alleles (*CYP2C19\*1*), which may result in reduced platelet inhibition.<sup>26,27</sup> This may result in a higher rate of adverse cardiovascular events.<sup>28</sup> Additional polymorphisms in *ABCB1* (a gene encoding the P-glycoprotein pump responsible for transporting molecules across intracellular and extracellular membranes) and *CYP3A4* can also reduce the effectiveness of clopidogrel and have been linked to adverse events.<sup>29</sup> However, there is

insufficient evidence to recommend routine genetic testing. Tests are available to determine the *CYP2C19* genotype and may be used to determine therapeutic strategy (i.e., alternative treatment may be considered if the patient is identified as a poor metabolizer). Functional testing (e.g., the VerifyNow *P2Y12* assay) can be done after the initiation of treatment to determine a patient's clinical responsiveness to clopidogrel (i.e., assess for a non-responder) and to further optimize antiplatelet strategy.<sup>30,31</sup> The GRAVITAS trial, however, did not show any benefit in individualizing the dose of clopidogrel in patients based on functional testing results.<sup>32</sup>

## Ticagrelor

### Mechanism of Action

Ticagrelor reversibly and noncompetitively binds the ADP *P2Y12* receptor reducing platelet aggregation. Due to the reversible nature of the receptor binding, the levels of platelet inhibition may fluctuate due to serum concentration of drug. It is metabolized via the cytochrome P450 enzyme system (the major isoenzyme is *CYP3A4*).<sup>33</sup>

### Indications and Dose

Ticagrelor is indicated for acute coronary syndrome (ACS) to reduce the rate of cardiovascular death, myocardial infarction (MI), and stroke. Ticagrelor reduces the rate of in-stent thrombosis in patients stented during treatment of ACS. Off-label indications include use in patients with UA/NSTEMI and an allergy to or intolerance of aspirin.

Ticagrelor is initiated with a loading dose of 180 mg followed by a maintenance dose of 60–90 mg twice daily ( $t_{1/2} = 7$  to 9 hours).<sup>34</sup> Time to maximal inhibition of platelet aggregation is approximately 2 hours.

### Side-Effect Profile

Side effects are similar to clopidogrel. Unique side effects specific to ticagrelor include elevated serum uric acid levels and transient dyspnea. Ticagrelor should, therefore, be used with caution in patients with a history of gouty arthritis or baseline hyperuricemia.<sup>35,36</sup> Dyspnea is typically self-limited and resolves within 1 week. It does not require any specific intervention nor does it warrant cessation of therapy unless the patient is intolerant to the medication-associated dyspnea.<sup>37</sup>

### Perioperative Management

As with clopidogrel, ticagrelor should be discontinued 7 to 10 days prior to elective surgery (minimum 5 days prior to procedure).

### Drug-Drug Interactions

Strong inducers of the cytochrome P450 enzyme system (specifically inducers of *CYP3A4*) may decrease serum drug concentrations and reduce platelet inhibitory activity. Some examples of commonly used *CYP3A4* inducers include barbiturates, anticonvulsants (e.g., phenytoin), and glucocorticoids. Caution should be exercised when combining these classes of medications.

## Prasugrel

### Mechanism of Action

Prasugrel is a prodrug that is activated by the *CYP450* enzyme system. Its active metabolite irreversibly blocks the *P2Y12* component of ADP receptors on the platelet surface, reducing platelet activation and aggregation.<sup>38</sup>

### Indications and Dose

Prasugrel is indicated for ACS managed with PCI or as an alternative for those patients intolerant to aspirin. It is contraindicated for use in patients with a history of transient ischemic attacks (TIAs) or stroke.<sup>38</sup> Patients are usually started with a loading dose of 60 mg followed by a maintenance dose of 10 mg daily. For patients weighing less than 60 kg, the daily dose is typically 5 mg/day. Prasugrel administration is not recommended for patients older than 75 years of age, though its use may be considered in high-risk situations.<sup>38</sup>

### Side-Effect Profile

As with other thienopyridines, the major adverse side effect is bleeding. Other specific side effects include hypertension, hyperlipidemia, and thrombotic TTP.<sup>39</sup>

### Perioperative Management

Similar to clopidogrel and ticagrelor, prasugrel should be discontinued 7 to 10 days prior to elective surgery (minimum 5 days prior to procedure).

## Cangrelor

### Mechanism of Action

Cangrelor reversibly binds to the *P2Y12* receptor to block ADP-induced platelet activation and aggregation.

### Indications and Dose

It is used during coronary intervention to reduce the risk of periprocedural myocardial infarction, and stent thrombosis in patients who were not previously taking another *P2Y12* inhibitor. The drug is administered with an intravenous 30 µg/kg bolus prior to PCI followed immediately by an infusion of 4 µg/kg per minute continued for at least 2 hours or for the duration of the procedure. The patient is then transitioned to an oral agent (clopidogrel, prasugrel, or ticagrelor) after the infusion is complete.

### Side-Effect Profile

The major side effect of cangrelor is bleeding. However, in the Champion Phoenix study, the incidence of bleeding was no different from that seen in patients on clopidogrel. Dyspnea or breathlessness was the other adverse effect associated with cangrelor use and occurred in 1.2% of patients compared with 0.3% of patients on clopidogrel ( $P < 0.001$ ).<sup>40</sup>

### Perioperative Management

Cangrelor is approved for use in the periprocedural period only. After a bolus, platelet inhibition is almost immediate

(<2 min). The half-life of cangrelor is 3 to 6 minutes, and platelet activity returns to normal within 60 minutes of cessation of the infusion.<sup>41</sup>

## GLYCOPROTEIN IIB/IIIA (GPIIB/IIIA) INHIBITORS

### Mechanism of Action

Three intravenous *GPIIB/IIIA*s are available for clinical use: abciximab, eptifibatide, and tirofiban. Abciximab is a monoclonal antibody against the *GPIIIB/IIIA* receptor, preventing activation and thus platelet aggregation. Eptifibatide and tirofiban, on the other hand, are peptide antagonists of the *GPIIIB/IIIA* receptor, which accomplish a similar effect in platelet inhibition.<sup>42,43</sup>

### Indications and Dose

Abciximab is indicated for the prevention of ischemic complications in patients undergoing PCI and patients with UA or non-ST-elevation MI scheduled to undergo PCI. It is administered intravenously as a loading dose of 0.25 mg/kg given prior to starting PCI followed by an infusion of 0.125 µg/kg per minute.<sup>43,44</sup>

Eptifibatide is indicated for patients with ACS who are to be managed medically or those undergoing PCI. It is administered intravenously with a bolus of 180 µg/kg followed by a continuous infusion of 2 µg/kg per minute.<sup>43,44</sup>

Tirofiban is indicated for patients with UA/non-ST-elevation MI to decrease the rate of adverse cardiovascular events. It is administered intravenously as a loading dose of 25 µg/kg followed by a continuous infusion dose of 0.15 µg/kg per minute.<sup>43,44</sup>

### Side-Effect Profile

The main adverse effect associated with all the *GPIIB/IIIA* modulators is bleeding, especially when these drugs are combined with other antiplatelet agents or anticoagulants. Other side effects associated with abciximab use include nausea, hypotension, and chest pain. Eptifibatide is associated with hypotension and tirofiban has been associated with coronary artery dissection. All the *GPIIB/IIIA* modulators are associated with thrombocytopenia. With abciximab, thrombocytopenia occurs in up to 5% of patients. Thrombocytopenia is less common with the two other agents (1% of patients).<sup>45</sup>

### Perioperative Management

Abciximab provides inhibition of platelet aggregation greater than 80% at 10 minutes after administration. It has a plasma half-life ( $t_{1/2}$ ) of 30 minutes; however, the dissociation half-life from the *GPIIB/IIIA* receptor can take up to 4 hours. Consequently, the infusion should be stopped at least 12 hours prior to surgery.<sup>46,47</sup>

Eptifibatide achieves more than 80% inhibition of platelet aggregation within 5 minutes after bolus dose and has a half-life of 2.5 hours. It should be stopped 2 to 4 hours prior to elective surgery.<sup>47</sup>

Tirofiban achieves inhibition of platelet aggregation greater than 90% within 10 minutes and has a half-life of 2 hours. It should also be stopped 2 to 4 hours prior to elective surgery.<sup>47</sup>

## PHOSPHODIESTERASE INHIBITORS

### Dipyridamole

#### Mechanism of Action

Dipyridamole inhibits the activity of adenosine deaminase and phosphodiesterase to increase the concentration of adenosine and cyclic adenosine monophosphate (*cAMP*), which promotes vasodilation and inhibits platelet aggregation. At baseline, dipyridamole alone is a relatively weak antiplatelet agent. A combination medication of dipyridamole and aspirin (Aggrenox) has been used for prophylaxis against stroke, and in symptomatic patients with carotid artery stenosis unsuitable for intervention.<sup>48,49</sup>

#### Indications and Dose

Dipyridamole is indicated as a pharmacologic agent for cardiac stress testing. The combination drug, Aggrenox, is indicated for stroke prevention.<sup>50–52</sup> Dipyridamole alone can be administered orally or intravenously. Oral doses are typically between 50 and 100 mg three to four times daily. The intravenous dosing for cardiac stress testing is usually 0.14 mg/kg per minute for 4 minutes with a maximum dose of 60 mg. Aggrenox contains 200 mg of dipyridamole and 25 mg of aspirin, and is administered twice daily.<sup>48</sup>

#### Side-Effect Profile

Oral administration has been associated with headache most commonly, but also dizziness, skin rash, and GI upset. Intravenous administration is associated with worsening chest pain, dizziness, or headache.<sup>48</sup> The vasodilatory effect of dipyridamole may adversely affect cardiac perfusion; therefore, caution should be exercised when using this medication in patients with established coronary disease. Contraindications to dipyridamole for cardiac stress testing include bronchospastic lung disease with ongoing wheezing or significant reactive airway disease, hypotension (SBP <90 mm Hg) or uncontrolled hypertension (SBP >200 mm Hg), ingestion of caffeine within 12 hours of the procedure, or UA, ACS, or recent acute MI.

#### Perioperative Management

The half-life of dipyridamole is 10 to 12 hours. Perioperative management of Aggrenox is dictated by the aspirin component, which produces irreversible *COX-1* inhibition to reduce platelet aggregation. This may be stopped 7 to 10 days in advance of surgery, if necessary.

### Cilostazol

#### Mechanism of Action

Cilostazol is a 2-oxoquinolone derivative and phosphodiesterase III inhibitor with vasodilatory and antiplatelet properties. It has also been reported to decrease proliferation of smooth

muscle cells and neointimal hyperplasia following endothelial injury. Taking cilostazol with food is recommended as the amount and rate of drug absorption is increased. Cilostazol is metabolized by CYP450 and excreted in urine therefore patients with renal disease have a prolonged half-life of the drug. Normal drug half-life is 11 hours.

### **Indications and Dose**

Meta-analysis of eight RCTs evaluating the efficacy of cilostazol shows that 50 mg BID or 100 mg daily of cilostazol increases maximum and pain free walking distance for patients with claudication compared with placebo. It can also prevent in-stent restenosis of femoropopliteal arteries. In patients with PAD, cilostazol has been shown to prevent thrombotic events. Addition of cilostazol can be considered in patients with persistent claudication despite treatment with aspirin, statin, and lifestyle modifications.

### **Side-Effect Profile**

Side effects can be severe and often a cause for discontinuation or noncompliance of cilostazol. Headaches, GI upset, diarrhea, dizziness, tachycardia and palpitations are reported. In patients with heart failure, cilostazol is contraindicated due to risk of ventricular tachycardia.

### **Perioperative Management**

General consensus recommends cilostazol should be stopped 2–3 days prior to elective surgery although the bleeding risk with cilostazol is reported at less than 1% and this drug can be continued up to surgery in high-risk patients requiring dual antiplatelet therapy (DAPT).

## **PROTEASE-ACTIVATED RECEPTOR-1 INHIBITORS**

### **Vorapaxar**

#### **Mechanism of Action**

Vorapaxar is a reversible antagonist of the protease-activated receptor-1 (*PAR-1*) to inhibit thrombin-induced and thrombin receptor agonist peptide (*TRAP*)-induced platelet aggregation.<sup>53,54</sup> It achieves 80% or greater inhibition of *TRAP*-induced platelet aggregation within 1 week of starting therapy and has a half-life of 3 to 4 days.<sup>54</sup>

### **Indications and Dose**

Vorapaxar is indicated to reduce adverse cardiovascular events in patients with a history of MI or with peripheral arterial disease (PAD).<sup>55,56</sup>

The approved dose of vorapaxar is 2.5 mg (vorapaxar sulfate) orally once daily in combination with aspirin and/or clopidogrel.<sup>56</sup>

### **Side-Effect Profile**

Bleeding is the major adverse effect associated with vorapaxar use. In the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2P)

study, any degree of bleeding was found in 25% of patients. Clinically significant bleeding (any bleeding requiring medical attention, including intracranial hemorrhage [ICH] or overt signs of bleeding with a drop in hemoglobin of  $\geq 3$  g/dL), occurred in 13.4% of patients.<sup>56</sup> Also, patients with a history of ischemic stroke had higher rates of ICH on vorapaxar compared with placebo. Consequently, vorapaxar is contraindicated in patients with a history of stroke, TIA, or ICH.<sup>56</sup> Other, less common side effects include anemia, depression, and rash.<sup>57</sup>

### **Atopaxar**

Similar to vorapaxar, atopaxar is a selective *PAR-1* antagonist that blocks thrombin-mediated platelet activation. During phase II trials, atopaxar-treated patients had increased bleeding events, elevated liver enzymes and QT interval prolongation. Therefore, atopaxar development was discontinued.

## **CLINICAL USE OF ANTIPLATELET AGENTS IN VASCULAR DISEASE**

### **Cardiovascular Death, Stroke, or Myocardial Infarction**

The primary prevention of cardiovascular disease using antiplatelet agents is controversial. The most recent CHEST guidelines from 2012 recommend the use of low-dose aspirin (75 to 100 mg) over no aspirin in patients aged 50 years or older without symptomatic cardiovascular disease. This recommendation was based on the 2009 Antithrombotic Trialists collaboration study demonstrating a reduction in nonfatal MI (low-risk patients had 6 fewer MIs per 1000 patients treated, moderate-risk patients had 19 fewer nonfatal MIs per 1000 treated, and high-risk patients had 31 fewer nonfatal MIs per 1000 treated) and improved total mortality (six fewer deaths per 1000 treated in low-risk and moderate- to high-risk groups) in patients taking aspirin based on a 10-year risk estimate using the Framingham risk score. There was, however, an increase in major bleeding in all groups taking aspirin compared with those not taking aspirin.<sup>12,58</sup> In a more recent meta-analysis, aspirin reduced the incidence of cardiovascular events by 10%, driven mostly by a significant reduction in nonfatal MI. Cardiovascular death was not improved with intake of aspirin, and the incidence of bleeding was significantly higher in those patients. Consequently, the authors were not able to make a recommendation for aspirin use in the primary prevention of cardiovascular disease.<sup>59</sup>

In 2019, the American College of Cardiology (ACC) and American Heart Association (AHA) Guidelines on the Primary Prevention of Cardiovascular Disease made three recommendations<sup>60</sup>:

1. Low-dose aspirin might be considered for primary prevention of atherosclerotic cardiovascular disease (ASCVD) in select higher ASCVD adults aged 40–70 years who are not at increased bleeding risk.

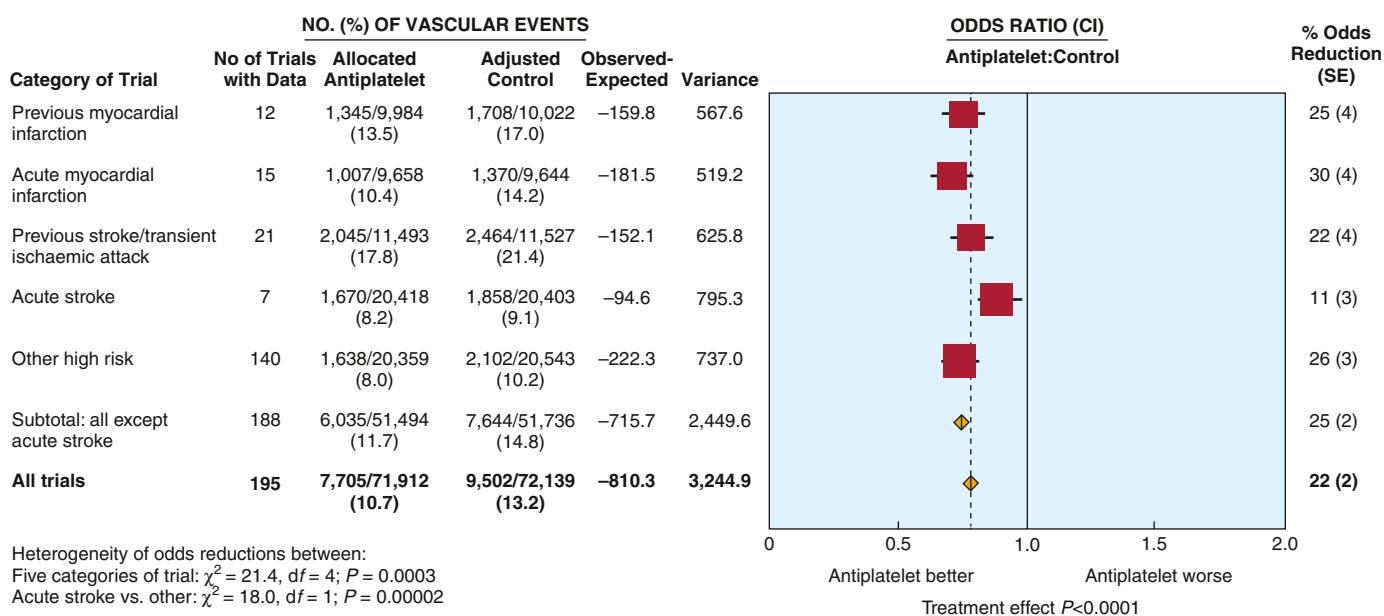


Figure 42.2 Proportional Effects of Antiplatelet Therapy on Vascular Events.<sup>9</sup>

- Low-dose aspirin should not be administered on a routine basis for primary prevention of ASCVD among adults  $>70$  years.
- Low-dose aspirin should not be administered for primary prevention among adults at any age who are at increased bleeding risk.

Secondary prevention of adverse cardiovascular events in patients who have survived an occlusive episode is well validated.<sup>9,61</sup> Antiplatelet therapy reduced subsequent vascular events by 25% in patients with previous MI, by 30% in patients with an acute MI, by 22% in patients with previous CVA/TIA, and by 11% in patients with acute CVA (Fig. 42.2). The positive effects were independent of the aspirin dose used.<sup>9,62</sup>

The CAPRIE trial compared clopidogrel to aspirin in 19,185 patients with recent stroke, MI, or symptomatic PAD. The study found that patients treated with clopidogrel had an annual 5.32% risk of stroke, MI, or death compared with 5.83% in patients treated with aspirin (8.7% relative risk reduction favoring clopidogrel).<sup>23</sup>

It should be noted that there is some evidence that the sudden discontinuation of aspirin therapy may be associated with an increased risk of thrombotic events, especially within the first 5 to 7 days. These include ACSs, stent-associated thrombosis, acute MI, ischemic stroke, and limb ischemia. Although further study is needed, it appears that aspirin withdrawal may be associated with a prothrombotic state.<sup>63</sup>

## Peripheral Artery Disease

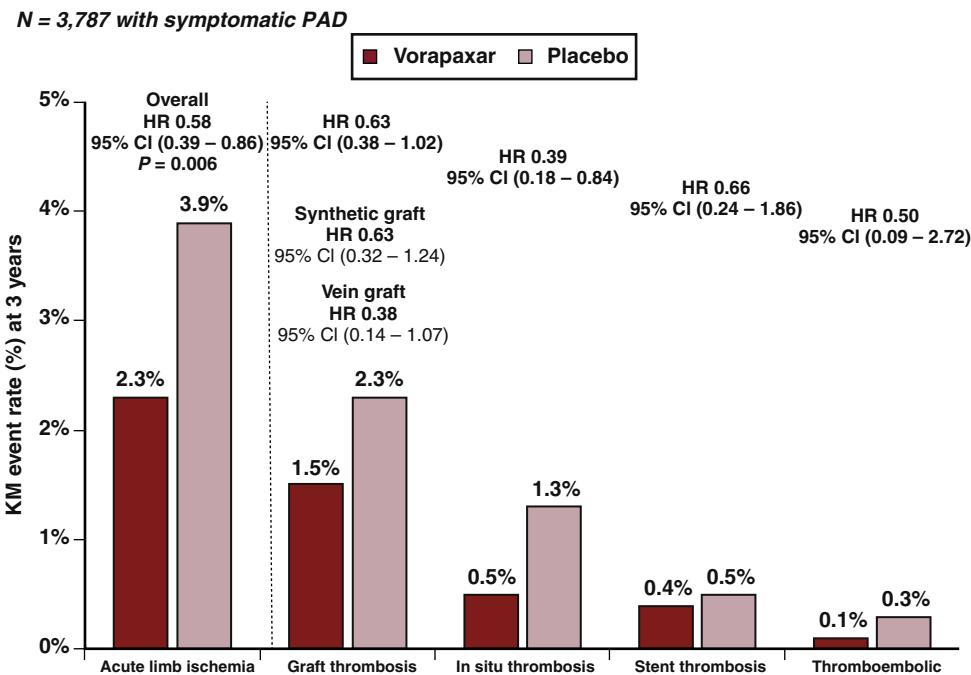
The 2017 European Society of Cardiology Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases have made the following recommendations related to antiplatelet therapy based on a large review of the most current data: (1) symptomatic and asymptomatic lower extremity arterial disease patients should be treated with antiplatelet monotherapy

(aspirin or clopidogrel); (2) symptomatic and asymptomatic carotid artery disease patients should be treated with antiplatelet monotherapy; (3) surgical revascularization of lower extremities or carotid arteries should be treated with antiplatelet monotherapy; (4) endovascular revascularization of lower extremities or carotid arteries should be treated with one month of DAPT (aspirin plus clopidogrel) and transitioned to monotherapy one month thereafter. In conjunction with the above recommendations, lifestyle risk factor modification remains paramount and all patients should be counseled on smoking cessation, increased physical activity and consideration of a plant-based diet.<sup>60</sup>

The STOP-IC study randomly assigned 200 patients to receive aspirin alone or aspirin plus cilostazol following percutaneous angioplasty with provisional nitinol stenting of femoropopliteal lesions. Angiographic restenosis was evaluated at 12 months. The aspirin plus cilostazol group had significantly less angiographic restenosis (20% vs. 49%) noted at 12 months. A small randomized study revealed decreased target lesion revascularization 6 months after initial endovascular revascularization but at 12 months there was no difference. The CASPER trial demonstrated benefit for prosthetic femoral to below-knee popliteal bypass treated with DAPT (aspirin plus clopidogrel) versus aspirin alone for outcomes of graft occlusion, amputation, death, and ipsilateral revascularization.

The TRA 2P trial assessing vorapaxar for the secondary prevention of ischemic events enrolled patients with stable atherosclerotic disease, including recent MI, CVA, and symptomatic PAD (claudication with an ABI  $\leq 0.85$  or previous revascularization for ischemia).<sup>56</sup> The patients with symptomatic PAD were studied separately regarding specific limb efficacy endpoints including acute limb ischemia (ALI), the need for peripheral revascularization (urgent and elective), or hospitalization for any vascular cause of an ischemic nature. Vorapaxar,

## VORAPAXAR AND ACUTE LIMB ISCHEMIA BY ETIOLOGY



**Figure 42.3** Vorapaxar and acute limb ischemia by etiology.<sup>64</sup> CI, confidence interval; HR, hazard ratio; KM, Kaplan–Meier; PAD, peripheral arterial disease.

in combination with other antiplatelet agents, reduced the risk of hospitalization for ALI (2.3% vs. 3.9%) and the need for peripheral revascularization (18.4% vs. 22.2%) compared with placebo, respectively.<sup>55</sup> A follow-up study on ALI in this patient cohort showed that vorapaxar reduced the risk of a first ALI event by 42% and reduced total ALI events by 41% compared with the placebo arm. This reduction was evident for all etiologies of ALI (graft thrombosis, in situ thrombosis, stent thrombosis, or thromboembolism; Fig. 42.3).<sup>64</sup>

The ongoing LONGDAPTPAD trial will attempt to elucidate the impact of 12 months DAPT (clopidogrel plus aspirin) versus 3 months of DAPT following percutaneous lower extremity angioplasty with endpoints of cardiac death, MI, stroke, coronary or carotid revascularization and major adverse limb events. Major and minor bleeding will be evaluated as well. The results of this trial may have an impact on the management of DAPT in revascularization patients.<sup>65</sup>

The VOYAGER PAD study published in 2020 was a double-blind randomized trial for patients undergoing lower extremity revascularization to receive rivaroxaban (2.5 mg BID) plus aspirin or aspirin plus placebo. Composite primary endpoints were major amputation, acute limb ischemia, ischemic stroke, myocardial infarction or cardiovascular death. Major bleeding was the primary safety outcome. Composite primary outcomes predicted by Kaplan–Meier estimates at three years were significantly less in the rivaroxaban group vs. the aspirin group. (17.3% vs. 19.9%). However, major bleeding events were increased in the rivaroxaban group vs. aspirin

group (5.9% vs. 4.0%).<sup>66</sup> This data can be used on a patient by patient basis when they are risk stratified for ischemia and bleeding events.

The COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategy) Trial compared three groups in patients with PAD (ABI less than 0.9), carotid artery disease or coronary artery disease. Patients were randomized to low-dose rivaroxaban (2.5 mg BID) plus aspirin (100 mg daily) or full dose rivaroxaban plus placebo or aspirin plus placebo. Stroke, myocardial infarction and cardiovascular death were the primary endpoints. A peripheral endpoint of major limb events including amputations was also evaluated. The rivaroxaban plus aspirin group had significantly lower primary endpoints (5% vs. 7%) and less major limb events (1% vs. 2%,  $P=0.0037$ ) compared to the aspirin alone group.<sup>67</sup>

While the COMPASS and VOYAGER PAD trials do involve anticoagulation, this demonstrates the evolving medical management of complex vascular patients requiring antiplatelet therapy. Despite some new evidence focused on PAD outcomes, the main indication for the use of antiplatelet agents in peripheral artery disease remains to reduce the risk of cardiovascular death, stroke, and MI.

## Carotid Artery Disease

It is well published and accepted that antiplatelet therapy decreases risk of stroke in patients with either symptomatic or asymptomatic atherosclerotic carotid artery stenosis (see

**Ch. 92, Cerebrovascular Disease: Decision Making Including Medical Therapy).** Aspirin is the most well studied antiplatelet therapy and low dose (75–150 mg) is equally effective to higher doses. In patients without known carotid stenosis who present with TIA or stroke, early aspirin administration is shown to be safe and effective. The CARESS and CHANCE trials<sup>68,69</sup> both demonstrated a benefit from DAPT (aspirin plus clopidogrel) in patients with symptomatic carotid artery stenosis for acute secondary stroke prevention. The SVS recommends antiplatelet therapy in asymptomatic patients to reduce overall cardiovascular morbidity and for secondary stroke prevention.<sup>70</sup>

While no large studies have demonstrated improved outcomes with DAPT and carotid artery stenting, two small studies have shown benefits and robust results from coronary angioplasty have driven this management strategy as well. The SVS recommends DAPT (aspirin plus clopidogrel or ticlopidine) at least 3 days prior to carotid artery stenting and continued for one month with aspirin therapy for life.

The SVS also recommends patients undergoing carotid endarterectomy should continue aspirin in the perioperative period and for life to reduce stroke and MI risk.<sup>70</sup>

## PERIOPERATIVE MANAGEMENT OF DUAL ANTIPLATELET THERAPY

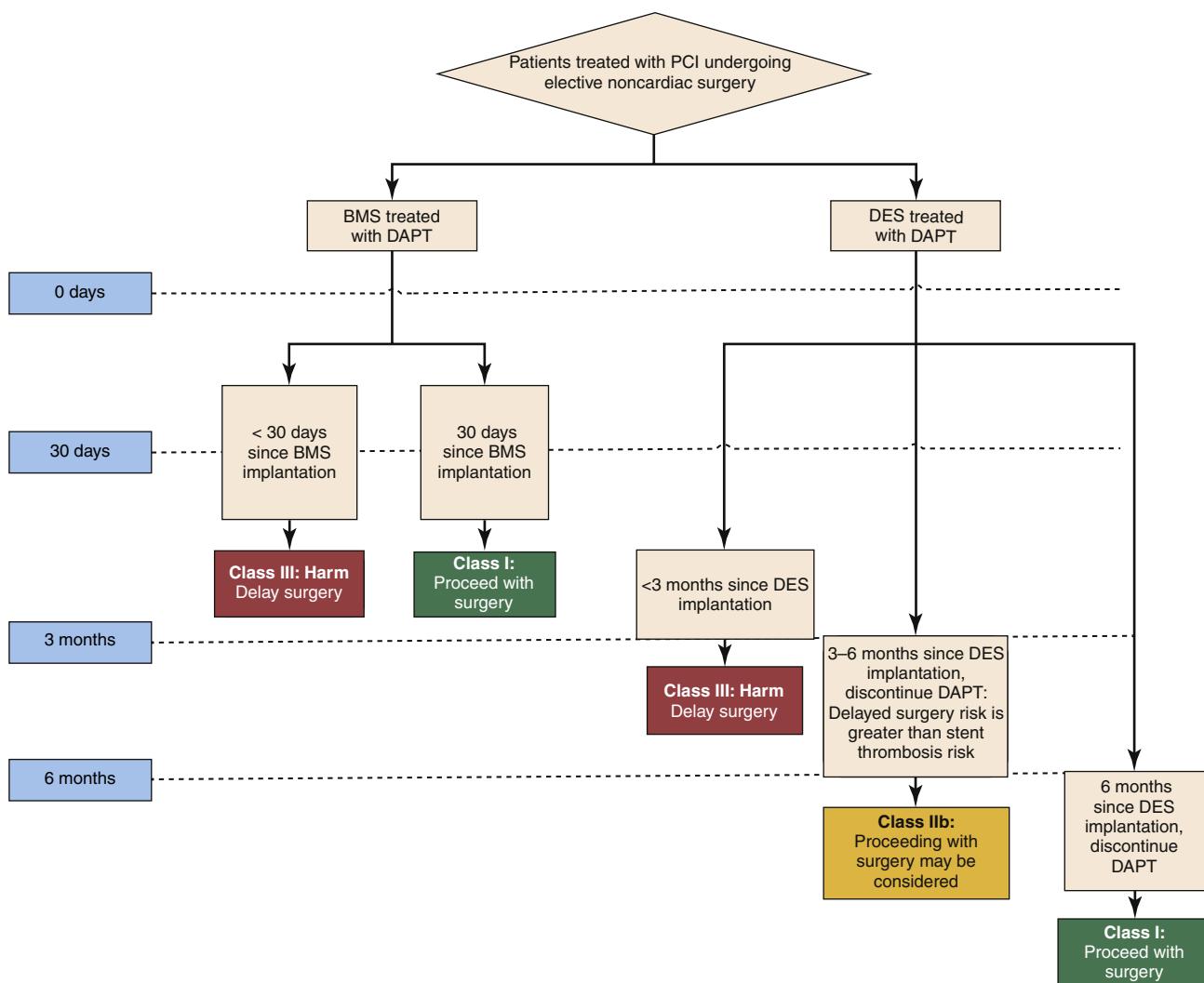
DAPT generally refers to a combination of aspirin and a *P2Y12* inhibitor (a thienopyridine), such as clopidogrel. Patients with a coronary artery disease (CAD) and history of MI are at an increased risk of recurrent infarctions as a result, in part, of enhanced platelet activation. Aspirin alone suppresses only one pathway of platelet activation. DAPT suppresses more than aspirin alone and has been shown to improve cardiovascular endpoints in patients with CAD. Coronary artery stenting is done with either bare-metal stents or drug-eluting stents (DESs). The 2014 AHA/ACC guidelines recommended DAPT in all patients with bare-metal coronary stents for at least 30 days after implantation. Discontinuing DAPT before 30 days is associated with an increased risk of stent thrombosis, adverse cardiovascular events, and mortality.<sup>63</sup> Thus the timing of procedures should take this risk into account. Elective procedures should be delayed until after the first 30 days after bare-metal stent implantation. For urgent, emergent, or nonelective operations, DAPT should generally be continued within the first 30 days after stent implantation unless the bleeding risk associated with the procedure is thought to be higher than the risk of stent thrombosis or

adverse cardiovascular events. In these cases, aspirin alone should be continued.<sup>71</sup>

First-generation DESs were sirolimus- or paclitaxel-eluting stents. The newer DESs use everolimus or zotarolimus. The 2014 AHA/ACC guidelines for patients with DES recommended therapy for 12 months.<sup>71</sup> This recommendation was formed from the evidence of stent thrombosis within the first 3 to 6 months in the first generation of DESs.<sup>72–74</sup> More recent studies on the newer generation of DESs have shown that they are associated with a lower risk of stent thrombosis.<sup>75,76</sup> A 2016 update to the AHA/ACC guidelines recommends that elective surgery be delayed for 3 months in patients treated with newer-generation DESs (Fig. 42.4).<sup>76</sup> For patients treated with greater than 3 months of therapy, DAPT may be discontinued for the procedure, if necessary, however with a slightly increased risk of thrombosis within the 3- to 6-month time frame. After 6 months, DAPT is safe to discontinue for procedures. In all cases, aspirin should be continued throughout the perioperative period, if possible. DAPT should be resumed as soon as the perioperative bleeding risk is considered low.<sup>77</sup>

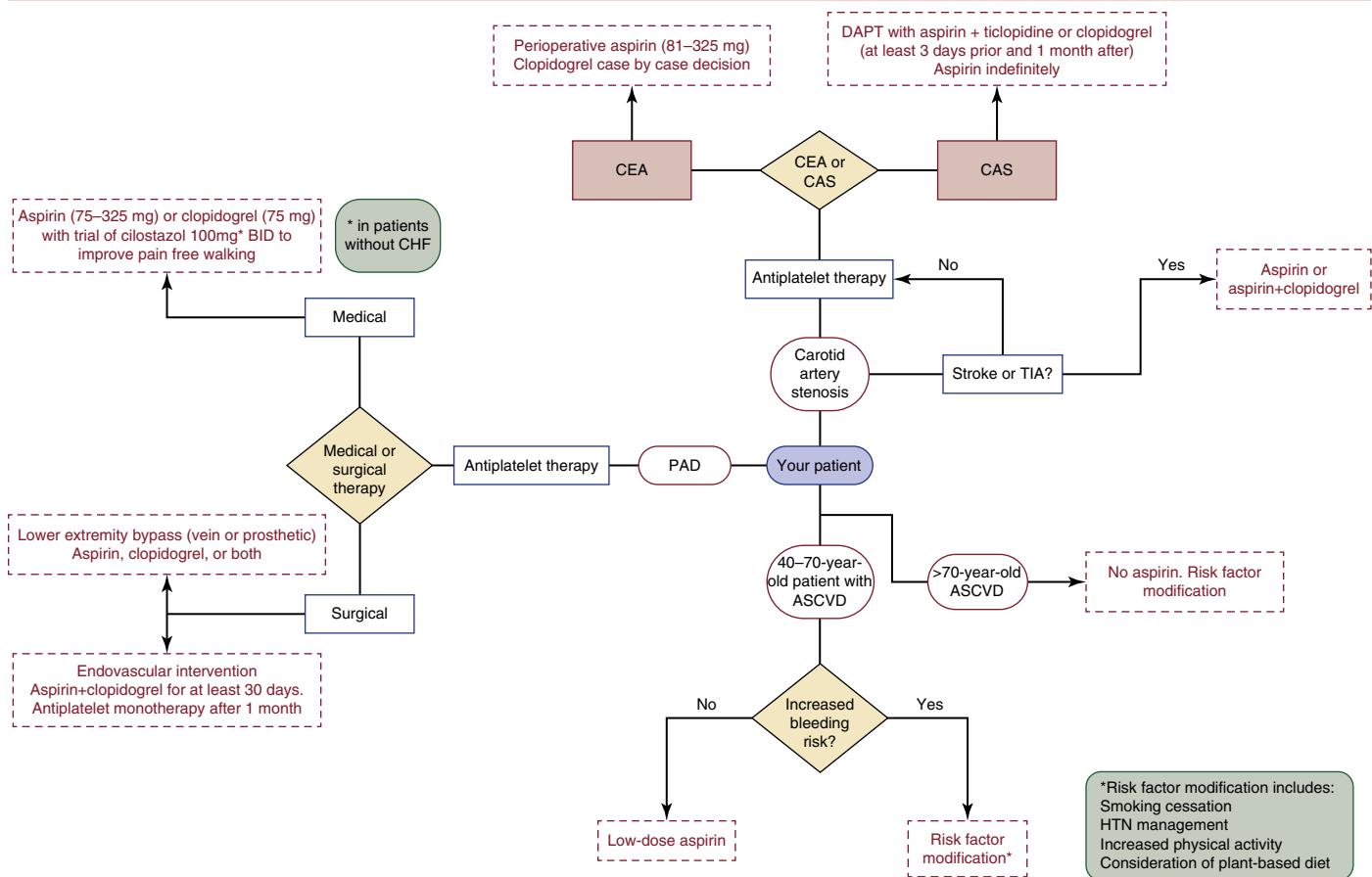
For patients who require urgent or emergent surgery before the recommended minimum duration of DAPT, the risk of discontinuing the DAPT should be weighed against the risk to the patient of not undergoing the procedure. Proposed strategies to limit the risk of adverse cardiovascular events or perioperative bleeding include perioperative platelet transfusion and “bridging” with an intravenous platelet inhibitor. Platelet transfusion may be used to stem the risk of bleeding in patients with DAPT; however, no studies have been performed to develop an optimal management strategy. Perioperative intravenous antiplatelet bridging has been studied, but has not been proven to eliminate the risk of stent thrombosis and may be associated with a higher incidence of bleeding complications.<sup>78,79</sup>

The long-term duration of DAPT has been a focus of more recent studies. The Dual Antiplatelet Study (DAPT study) assessed 12 months versus 30 months of DAPT after coronary stenting. It showed a significant reduction of late coronary stent thrombosis and less major adverse coronary or cerebrovascular events in patients treated with DAPT compared with aspirin alone. In patients with bleeding complications, or with a relatively increased risk of bleeding (e.g., history of TIA or stroke, age  $\geq 75$  years, recent trauma or surgery, recent or recurrent GI bleeding, active peptic ulcer disease, severe hepatic impairment, body weight  $< 60$  kg, or use of oral anticoagulants), consideration can be given for treatment for less than 12 months with DAPT.<sup>76,80</sup>



**Figure 42.4** 2016 ACC/AHA Guidelines for Perioperative Management of Dual Anti-Platelet Agents in patients undergoing noncardiac surgery. *BMS*, bare-metal stent; *DAPT*, dual antiplatelet therapy; *DES*, drug-eluting stent; *PCI*, percutaneous coronary intervention.

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# Thrombolytic Agents

ANASTASIA PLOTKIN and FRED A. WEAVER

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## INTRODUCTION

Embolic and thrombotic events in the arterial and venous systems lead to end-organ malperfusion and dysfunction. In the past, open surgical procedures were used to restore vessel patency and organ function; however, with the advent of thrombolytic agents and endovascular techniques, intravenous thrombolysis (IVT) and catheter-directed thrombolysis (CDT) have become essential components in the contemporary management of acute arterial and venous thromboembolic conditions.

Thrombolytic agents have evolved over time, with many of the original agents (streptokinase [SK] and urokinase [UK]) no longer manufactured in the United States, even while still holding Food and Drug Administration (FDA) labels for use. In current practice, alteplase (recombinant tissue plasminogen activator [rt-PA]) is the agent most commonly used. Current FDA indications for thrombolysis include acute myocardial infarction (AMI),<sup>1–4</sup> pulmonary embolism (PE),<sup>1,2,5</sup> acute ischemic stroke (AIS),<sup>2</sup> arterial thrombosis and embolization,<sup>1</sup>

deep venous thrombosis (DVT),<sup>1</sup> and central venous catheter occlusion (Table 43.1).<sup>2</sup>

## HISTORY

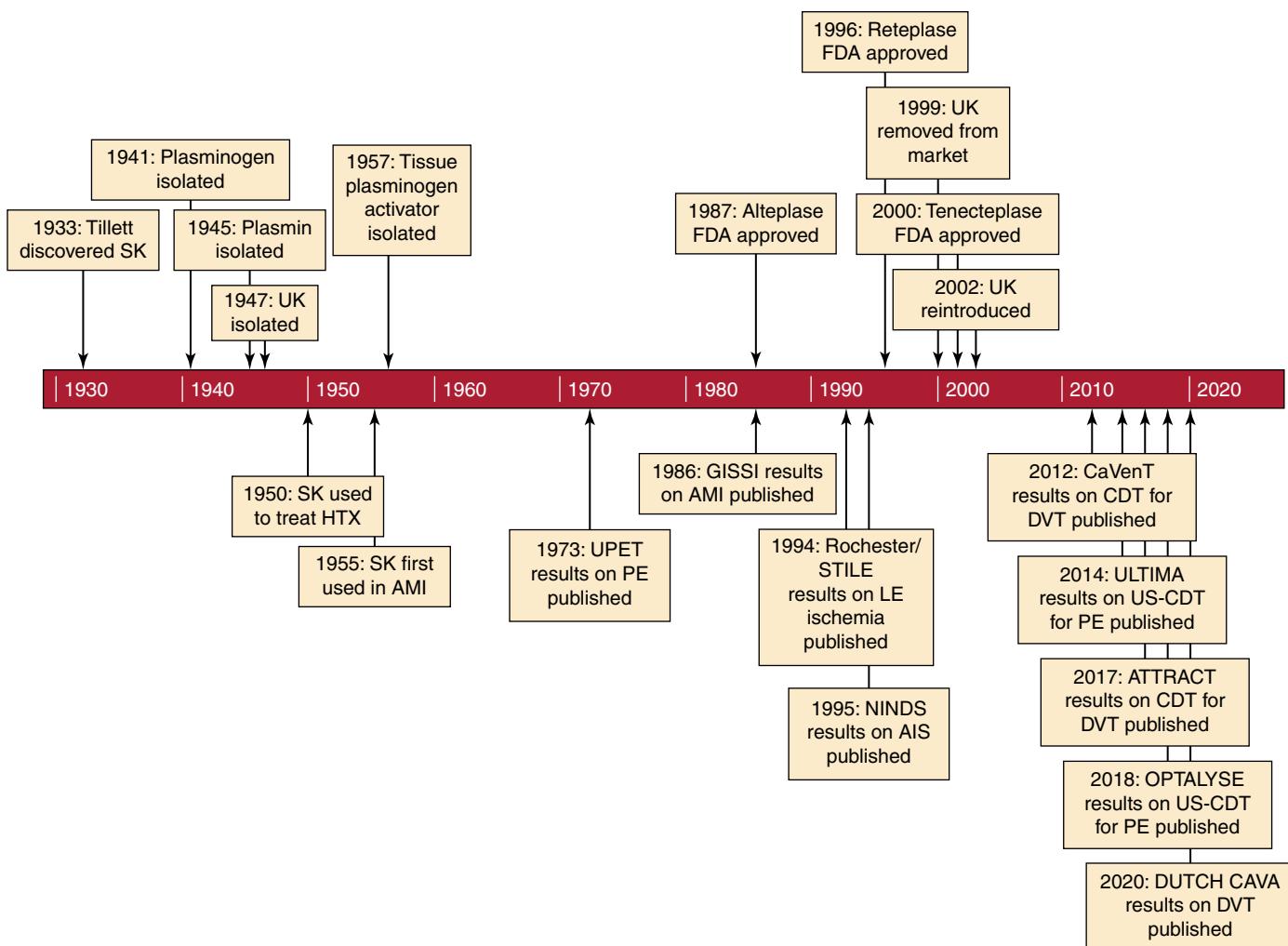
Early theories on the method of clot lysis arose from observations of postmortem blood, which was found to exist in both liquid and coagulated forms. In 1769, Morgagni noted this phenomenon occurred after traumatic death,<sup>6</sup> and in 1906 Morawitz found that postmortem liquid blood contained no fibrinogen and could liquefy coagulated blood.<sup>7</sup> It was postulated that an “inactive component” of blood, controlled by a “regulator,” could be converted into a “fibrin-degrading agent.”

The “inactive component” was first described by Milstone in 1941 as “lytic factor,” now known as plasminogen.<sup>8</sup> Subsequently, Kaplan and Christensen separately identified the “fibrin-degrading agent” as plasmin.<sup>9–11</sup> The “regulator,” or tissue plasminogen activator (t-PA), was the last to be isolated in 1957 by Albrechtsen<sup>12</sup> (see Ch. 38, Normal Coagulation).

**TABLE 43.1** Thrombolytic Agents and Indications Approved by the US Food and Drug Administration

Generic Name	Trade Name	Manufacturer	FDA Indication
Streptokinase <sup>a</sup>	Streptase	CSL Behring (King of Prussia, Pennsylvania)	AMI, PE, DVT, peripheral arterial thrombosis or embolism
	Kabikinase	Pharmacia & Upjohn AB	
Urokinase <sup>a</sup>	Kinlytic	Microbix Biosystems (Ontario, Canada)	PE
Alteplase	Activase	Genentech (South San Francisco, California)	AMI, PE, stroke
	CathFlo Activase	Genentech	Central venous catheter occlusion
Reteplase	Retavase	Cornerstone Therapeutics (Cary, North Carolina)	AMI
Tenecteplase	TNKase	Genentech	AMI

<sup>a</sup>Though still FDA approved, no longer available in the United States. AMI, acute myocardial infarction; DVT, deep venous thrombosis; FDA, US Food and Drug Administration; PE, pulmonary embolism.



**Figure 43.1** Timeline of Key Moments in Thrombolytic History. AMI, acute myocardial infarction; AIS, acute ischemic stroke; FDA, US Food and Drug Administration; GISSI, Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico; HTX, hemothorax; LE, lower extremity; NINDS, National Institute of Neurological Disorders and Stroke; PE, pulmonary embolism; SK, streptokinase; STILE, surgery or thrombolysis for the ischemic lower extremity; UK, urokinase; UPET, Urokinase Pulmonary Embolism Trial.

The discovery of the first thrombolytic agent, SK, came by chance at Johns Hopkins University in 1933 by Tillett. He observed that streptococcus in human plasma would agglutinate, whereas streptococcus in human serum did not. He hypothesized that fibrinogen, present in plasma but not in serum,

bound to the bacteria and caused agglutination. To test this hypothesis, he compared human plasma in test tubes as a control to human plasma in which streptococci were added. After addition of calcium, both tubes demonstrated clot formation. However, after the test tubes sat overnight, he noted the clot

had liquefied in the streptococcus-containing tube. He attributed this finding to the production of “fibrinolysin” by streptocci.<sup>13,14</sup> A year later he isolated “fibrinolysin,” which is now known as SK.<sup>15</sup>

In 1949, Tillett and Sherry reported the first clinical uses of SK in the thoracic cavity to treat empyema and retained hemothorax.<sup>16,17</sup> They reported the first human intravascular experience with SK in 1954.<sup>18,19</sup> Urokinase was the second thrombolytic agent discovered in 1946, with clinical application in 1961.<sup>20</sup> As experience with these two early agents grew and additional agents developed, large clinical trials encompassing many vascular applications soon followed, expanding the use of thrombolytic agents in clinical practice (Fig. 43.1).

## THROMBOLYTIC DRUG ADMINISTRATION

### Systemic/Intravenous Thrombolysis

When thrombolysis was first introduced, systemic delivery via a peripheral intravenous catheter was the only method of administration. Although this was effective in certain clinical scenarios, it required large doses of thrombolytic agents with an increased risk of hemorrhagic complications. The development of CDT has allowed a more targeted delivery of thrombolytic agents in smaller doses. However, IVT still remains a common mode of delivery in applications in which preservation of end organ function requires rapid delivery (AMI, AIS).

### Catheter-Directed Thrombolysis

CDT provides direct delivery of the thrombolytic agent into the thrombus.<sup>21,22</sup> It is the preferred method of delivery for acute limb ischemia,<sup>23,24</sup> DVT,<sup>25</sup> and arteriovenous graft (AVG) occlusion.<sup>26</sup> The endovascular techniques used for CDT also permit concomitant percutaneous treatment of the underlying culprit lesions responsible for vessel or graft occlusion.<sup>3</sup>

CDT requires traversal of the occluded arterial or venous thrombosis with a guidewire, followed by placement of a multiple side-hole infusion catheter. An initial bolus is delivered via pulse spray technique. Depending on the particular vessel and end organ being treated, a continuous infusion for a specified period of time follows. To maximize the effectiveness and minimize systemic delivery of the thrombolytic agents, the infusion catheter side holes should be placed within the thrombus. Heparin is used as an ancillary drug during CDT and commonly infused through the indwelling arterial sheath. Administration of heparin is crucial to prevent propagation of thrombus around the indwelling catheter.<sup>23,24,27</sup> Full anticoagulation with heparin with an activated partial thromboplastin time (aPTT) of 60 to 80 seconds should be achieved before thrombolysis, but once CDT has begun, the heparin dose should be decreased to 500 to 1000 U/h. The heparin drip should be adjusted to maintain an aPTT no more than 1.5 times control. Full anticoagulation with larger doses of heparin during CDT does not improve outcomes, and evidence suggests that excessive anticoagulation can potentiate bleeding complications.<sup>28</sup>

### Catheter-Directed Thrombolysis with Mechanical Thrombectomy

Percutaneous mechanical thrombectomy is a catheter-based therapy that disrupts the thrombus and allows better penetration of the clot by the thrombolytic agent. Its putative advantages include decreased thrombolytic dosing and shortened therapy time. Most mechanical devices were originally used for the treatment of AVG thrombosis,<sup>29</sup> but their use has been expanded to the peripheral vasculature (discussed in greater detail in Ch. 104, Acute Limb Ischemia: Surgical and Endovascular Treatment; Ch. 161, Iliocaval Venous Obstruction: Endovascular Treatment; and Ch. 162, Superior Vena Cava Obstruction and its Management).<sup>30</sup> A number of methodologies and devices exist for mechanical thrombectomy, each with advantages and disadvantages:

1. Hydrodynamic: Saline is infused and aspirated to create a local reduction in pressure (the Venturi effect).
2. Rotational recirculation: Rotating blades or propellers macerate the thrombus.
3. Mixing: Devices with a double-balloon catheter system confine the thrombolytic agent within a vessel, whereas a rotating, sinusoidal wire disrupts the clot.
4. Ultrasound: High-frequency, low-power ultrasound energy is delivered to loosen and separate fibrin strands to permit better penetration of the thrombolytic agent.
5. Aspiration: Aspiration of thrombus by a large suction catheter and syringe.
6. Magnetic targeting: External magnetic field is used to localize magnetic carriers within the administered drug and guide therapy to the thrombus.

### Biological Targeting

Biological targeting most frequently involves binding the thrombolytic agent to red blood cells (RBCs). The abundance, large size of RBCs, and high fibrin content provide beneficial characteristics as a drug delivery system.<sup>31</sup> A study using *in vivo* animal models by Murciano demonstrated that t-PA bound to RBCs was much more selective in lysing nascent thrombus than free t-PA in the lungs and other arteries.<sup>31,32</sup> Advantages include the potential for increased bioavailability and longer circulation. Disadvantages also include prolonged circulation, and the inability to lyse preexisting clot.<sup>33</sup> Therefore, at present RBC target therapy may serve as a prophylactic rather than a therapeutic agent. Further studies and trials are warranted to better evaluate these effects on other *in vivo* models and in humans.

### Monitoring

No existing laboratory test directly monitors the degree and effectiveness of thrombolysis. D-dimer and fibrin degradation products are elevated by thrombolysis, but levels do not correlate with the degree of thrombolysis. Thrombolytic therapy creates a dynamic fibrinolytic state consisting of both thrombus dissolution and thrombus formation. Formation occurs in an attempt to replace lysed clot, consuming coagulation factors

and fibrinogen in the process. If fibrinogen levels drop below 100 mg/dL (2.9 μmol/L) or the aPTT increases above 100 seconds, excessive consumption of coagulation factors is present and an increased risk of hemorrhagic complications exists. In these circumstances, it is prudent to reduce or temporarily stop the lytic infusion until fibrinogen levels increase or the aPTT decreases, or both.<sup>34</sup>

Other laboratory tests for indirect monitoring of the thrombolytic state include hemoglobin, platelet count, and creatinine, primarily to evaluate for signs of ensuing hemorrhagic complications. Patients treated by thrombolysis should be monitored in the intensive care unit or intermediate unit, where laboratory tests can be drawn at 4- to 6-hour intervals and patients assessed on an hourly basis.<sup>1–5,34</sup>

With CDT, serial angiography is performed through the indwelling catheter to assess the results of thrombolysis at 6- to 12-hour intervals over a 24- to 48-hour period. Restored pulse, Doppler signal, or improved symptoms can be surrogates for successful treatment. CDT should be discontinued once organ perfusion has been adequately restored, with subsequent transition to full anticoagulation with heparin.<sup>23,24,27</sup> Thrombolysis beyond the 48-hour window increases the risk of complications with little to no additional benefit.

## Complications

Complications of thrombolytic therapy can be classified as hemorrhagic, antigenicity-related, catheter-related, or embolic.

### Hemorrhagic

Bleeding is always a risk when thrombolysis is used. Major versus minor bleeding correlates with the degree of bleeding and resultant clinical consequences, but in general, major bleeding includes intracerebral, retroperitoneal, or gastrointestinal hemorrhage. Minor bleeding is usually at the CDT puncture site and managed with local measures.<sup>34,35</sup> Puncture-site bleeding can evolve into major bleeding if a large hematoma develops or if blood tracks into potential spaces such as the retroperitoneum. Ultrasound guidance can minimize multiple needle passes for vascular access and thus minimize this bleeding risk.

The risk of remote-site bleeding increases as more thrombolytic drug is administered leading to clotting factors and fibrinogen depletion. In general, patients treated for pathologies that require longer infusions have a higher bleeding risk. Acute limb ischemia, PE, and DVT use more total thrombolytic compared to AMI and AIS; AVG and catheter occlusion use the smallest doses.<sup>36</sup>

Intracerebral hemorrhage (ICH) is the most dreaded complication. AIS is associated with the greatest incidence of ICH (6.4% to 8.8%). Thrombolysis provides reperfusion of a stunned penumbra, but also lyses hemostatic plugs, leading to hemorrhagic reperfusion.<sup>37</sup> For other thrombolytic indications, the incidence of ICH varies depending on the thrombotic process: PE (0% to 4.5%), AMI (0.3% to 1.8%), and peripheral artery occlusion (1% to 2%).<sup>35,36</sup> The true incidence of other remote bleeding complications is difficult to determine given inconsistent definitions and reporting. When major bleeding is defined as that causing permanent disability, increased hospital stay, or a requirement for blood transfusion, rates as high as

27% have been noted.<sup>35,36</sup> Overall major bleeding after thrombolysis has been reported in 10% to 27% of patients with acute limb ischemia, 5% to 21% with PE, 0.3% to 5.9% with AMI, and 4% to 11% with DVT.

### Antigenicity Related

This complication is mainly related to SK. Minor allergic reactions have been reported in 1% to 10% of cases, and life-threatening allergic reactions in less than 0.01%.<sup>1</sup> Pretreatment with 100 to 250 mg of methylprednisolone, antihistamines, or acetaminophen (or any combination of these drugs) can reduce the allergic response.<sup>1</sup> Other thrombolytics, such as UK and rt-PA, are naturally found *in vivo*, thus allergic reactions are rare.<sup>2,5</sup>

### Catheter Related

Catheter insertion for CDT poses the same risks associated with any endovascular procedure, including but not limited to dissection of the artery, pseudoaneurysm, dislodgment of thrombus during wire or catheter manipulation, and bleeding around the introducer sheath.<sup>38</sup>

### Embolic

As a thrombus is lysed, fragments may embolize. Embolization is most often seen in patients with acute limb ischemia. Typically, after initial clinical improvement with restoration of a pedal pulse or Doppler signal, sudden clinical deterioration due to embolism occurs. In randomized clinical trials of patients with acute limb ischemia, embolic events occurred in 9% to 13% of patients. In most cases, advancing the catheter distally and continuing the thrombolytic infusion can effectively treat the embolic malperfusion.<sup>38–40</sup>

Embolic events occur less often in other applications. Clinically significant PE has been seen after thrombolytic treatment of DVT (0% to 10%); and though it is a hypothetical risk in catheter and AVG occlusion, PE has also been rarely reported (<1%).<sup>36</sup>

## Contraindications

Absolute contraindications to thrombolytic treatment include conditions that are likely to be associated with existing or very recent hemorrhage: (1) active internal bleeding; (2) recent (within 2 months) cerebrovascular accident, trauma, or intracranial or intraspinal surgery; (3) known intracranial neoplasm; (4) severe uncontrollable hypertension; (5) uncontrollable clotting disorders; and (6) previous severe allergic reactions to the thrombolytic agent.

Relative contraindications include: (1) recent (within 10 days) operative or obstetric procedures, biopsy, or procedure in a location that is not compressible, gastrointestinal bleeding, or trauma, including cardiopulmonary resuscitation; (2) left heart thrombus; (3) subacute bacterial endocarditis; (4) severe liver or kidney disease; (5) diabetic hemorrhagic retinopathy; (6) acute pancreatitis; (7) pregnancy; and (8) any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage due to its anatomic location.<sup>1,2,5,27</sup>