Despite routine usage in peripheral interventions, the indications, type, and duration of anticoagulation remains very dependent on the individual practitioner. In addition to the use of heparinized saline for flushes, anticoagulation is systemically utilized during many studies. Although heparin remains the most common anticoagulant used, newer anticoagulants and lessons learned from percutaneous coronary interventions (PCIs) are rapidly influencing clinical decisions regarding anticoagulation.

Any intervention upon a vessel exposes the subendothelium to circulating blood elements. Most specifically, tissue factor is exposed to factor VII, thus beginning the coagulation cascade (Figure 1).

**WHY ANTICOAGULATE?**

All elements of Virchow’s triad are encountered during endovascular diagnosis and therapy. Thromboembolic risk due to vessel trauma is elevated as the duration and complexity of the procedure increases, and as the vessel size decreases. Anticoagulation is utilized to prevent thrombosis above the level of vessel occlusion (ie, angioplasty, aortic occlusion during endograft placement). In addition, the presence of a foreign body (ie, sheath, catheter) also serves as a nidus for thrombus formation. The closer the outer diameter of a sheath approaches the inner diameter of the artery it enters, the higher the thrombotic risk will be due to stasis. In addition, many patients who require endovascular therapies may have a hypercoagulable state. Up to 10% of patients undergoing peripheral vascular procedures were found to have a hypercoagulable state, and there is evidence that platelets of patients with peripheral vascular disease are overactive. Despite all of these indications, in peripheral vascular intervention, there is a lack of evidence-driven data to assist in indications for anticoagulation, choice of anticoagulant, and duration of anticoagulant therapy. Most current understanding and practices are derived by extrapolating data from PCI to peripheral interventions.

Agents fall into two broad categories—antiplatelet agents and inhibitors of the coagulation cascade.

Figure 1. Current understanding of the coagulation cascade with tissue factor as the instigator of the enzymatic chain reaction.
ANTIPLATELET AGENTS

Aspirin

The most commonly used antiplatelet agent remains aspirin (acetylsalicylic acid). A aspirin irreversibly inhibits cyclo- oxidase, blocking the synthesis of the platelet agonist prostacyclin. The minimum dose of aspirin is 80 mg to 300 mg administered at least 2 hours before PCI. Although clinically effective, aspirin is a weak antiplatelet agent and does not inhibit any of the other platelet agonists (thrombin, adenosine diphosphate, epinephrine, serotonin).

Clopidogrel

Clopidogrel is an inhibitor of adenosine diphosphate (ADP), preventing the binding of this potent platelet agonist. Multiple studies have evaluated the benefit of combining ADP inhibition with cyclo-oxidase inhibition. Pretreatment with ADP inhibition prior to coronary stenting improves patency and reduces periprocedural infarction. An effective dose of clopidogrel is 300 mg, although many clinicians use 75 mg. The optimal duration of this therapy after stenting is unclear. It seems that a minimum of 1 month is required. As is also true of aspirin, the effect of clopidogrel is irreversible. For both drugs, there must be turnover of platelets in the absence of active drug to restore platelet function. This generally takes at least 5 days.

Both aspirin and clopidogrel inhibit the activation and adhesion of platelets, both of which are early events. The final step in platelet aggregation is the cross-linking of platelets across fibrinogen, which allows the platelet phospholipid membrane to serve as a scaffold for larger reactions of the coagulation cascade. This occurs via interaction between fibrinogen and platelet surface receptors. The specific receptor is a dimer of glycoproteins IIa and IIb (IIb/IIIa receptor, integrin IIb/IIIa, GP2b3a). Development of IIb/IIIa inhibition was a major step in improving outcomes from PCI. The first agent, abciximab is a monoclonal antibody fragment that binds to the glycoprotein IIb/IIIa complex on the platelet membrane, preventing binding to fibrinogen. The drug is active within 2 hours after infusion, but has a prolonged effect. The clinical effect is reduced at 6 to 12 hours, but the blockade of platelet function remains detectable for up to 14 days. Newer agents, such as epifibatide, are more specific and are competitive inhibitors, resulting in a shorter clinical effect (12 hours for abciximab vs 2.5 hours for epifibatide). Abciximab is approved by the FDA for administration in acute coronary syndromes as well as PCI, and epifibatide is approved for use only during PCI. Abciximab was found to reduce death rates, myocardial infarction, and the need for urgent revascularization at 30 days, 3 months, and 6 years. This improvement, however, comes at the cost of increased bleeding complications.

COAGULATION-CASCADE INHIBITORS

Heparin

Heparin was introduced into clinical use in 1935. It remains the most common anticoagulant in use today, and it is estimated that 30% of all patients admitted to a hospital receive some form of heparin. The most commonly used form is unfractionated heparin (UFH), which is a mixture of polysaccharide chains. Heparin complexes with endogenous antithrombin and inactivates coagulation factors X, XII, Xla, and IXa. UFH is quickly available after intravenous administration (within 3 minutes) and its effect is easily assessed by way of the activated clotting time (ACT).

Duration of action depends on the dose administered, but is roughly 60 minutes. The activated partial thromboplastin time (aPTT) is used to monitor longer-term therapy. Heparin has an antidote in protamine, which complexes with heparin in a ratio of 1 mg protamine to 100 units (U) of heparin and prevents the binding of heparin to antithrombin. The indirect activity of heparin represents a major drawback to its use. In addition, heparin is ineffective against existing thrombus, and has significant biologic variability. There are no firm recommendations regarding dosing of heparin for endovascular interventions. High-risk interventions (brachiocephalic, small vessels) may benefit from administration of 75 to 100 U/kg during balloon angioplasty, whereas straightforward aortoiliac interventions may only require doses of 25 to 50 U/kg. However, lower doses may be safe. One study demonstrates safety and efficacy of roughly 50 U/kg for coronary interventions. The implication is that for small-vessel interventions, lower doses may be sufficient.

Low-Molecular-Weight Heparin

Low-molecular-weight heparins (LMWHs) are shorter segments of depolymerized UFH. There are several available clinically, and they are differentiated by the specific fraction utilized in the preparation and slight differences in anticoagulant strength. LMWHs offer more anti-Xa activity than the UFH and less anti-IIa activity. This theoretically leads to greater efficacy and lower bleeding complications. In addition, LMWHs are administered as a single subcutaneous injection, and do not require monitoring to determine anticoagulant ability due to more predictable biolog-
ic activity. However, the lack of a rapid method to assess anticoagulant adequacy is the major drawback of using LMWH. There are studies that show efficacy and safety of LMWH as the sole heparin administered for the purpose of PCI.15,16

**Lepirudin**

The prototype of direct thrombin inhibitors is lepirudin. Lepirudin is a recombinant derivative of hirudin, the anticoagulant present in the saliva of the medicinal leech. Lepirudin is a bivalent thrombin inhibitor, binding at both the catalytic site of thrombin (preventing the conversion of fibrinogen to fibrin), as well as binding at the fibrinogen binding site. Lepirudin is renally cleared, and its effect is markedly prolonged in patients with renal failure. There is no direct antidote for overdosage with lepirudin. These two facts limit its utility in patients with advanced renal insufficiency. The dose for patients with normal renal function is a bolus of 0.4 mg/kg followed by continuous infusion at 0.15 mg/kg per hour, and the half-life is approximately 80 minutes. The anticoagulant effect is monitored by the aPTT. It may also be monitored at point-of-care via ecarin clotting time. We have found lepirudin to be a safe and effective anticoagulant for patients with HAAb.21

Although some patients form antibodies against hirudin, 23 patients were prospectively studied, and 56% developed antibodies against hirudin as detected by enzyme-linked immunosorbent assay. However, no patient demonstrated resistance or other effects attributable to the anti-hirudin antibodies. Any clinical significance of these antibodies has yet to be shown.22

**Argatroban**

Argatroban is a small (527 d), synthetic, direct thrombin inhibitor derived from L-arginine. Unlike lepirudin, argatroban binds reversibly to the catalytic domain of thrombin. There is activity against both free and clot-bound thrombin, with no activity against factor Xa or plasmin.23 In a study of anticoagulation for PCI using historical controls (HIT patients treated with heparin), argatroban resulted in improved clinical outcomes and no increase in hemorrhagic complications.24 Standard dosing is 2 µg/kg per minute intravenously, and the drug is titrated to achieve an aPTT of 1.5 to 3 times control and may be monitored at point-of-care via ACT. Argatroban undergoes hepatic metabolism and excretion. It is a reversible inhibitor, with a half-life of 40 to 50 minutes, allowing rapid restoration of coagulation after infusion. Because it is not renally cleared, it has a predictable effect in patients with renal insufficiency.25 There is no specific antidote for argatroban and administration should be discontinued if suspicion of overdosage or hemorrhagic complication exists. In the setting of PCI, argatroban is approved for use in patients with HIT and has been used at a dose of 25 mg/kg per minute after a 350 mg/kg initial bolus and titrated to an ACT of 250 to 300 seconds. Results in these patients are comparable to historic heparin controls.24

**Bivalirudin**

Another direct thrombin inhibitor, bivalirudin, has been more extensively studied in PCI than the others,
but not in placebo-controlled trials. Bivalirudin has been studied in subtherapeutic doses (TIM I 7) and heparin-controlled trials (HERO 2, TIM I 8). In a large (5,674 patients) meta-analysis of six studies looking at outcomes after myocardial infarction, bivalirudin was associated with a significant reduction in the composite of death or infarction and in major hemorrhage.26 The Hirulog and Early Reperfusion or Occlusion-11 trial (HERO-11) evaluated early angiography in patients undergoing fibrinolysis, and the HERO-2 trial specifically evaluated bivalirudin in PCI. Grade 3 flow was achieved in 48% of patients versus 35% of patients who received heparin. Bivalirudin failed to reduce mortality but did reduce the reinfarction rate.27 The REPLACE-2 heparin. Bivalirudin failed to reduce mortality but did

CONCLUSION

In summary, although there are multiple studies in the cardiac literature, there is a dearth of studies specifically looking at interventions in the periphery. There are no firm consensus statements on dosage or preferred agent in any vascular tree. If the data from the coronary circulation can be extrapolated to the periphery, platelet inhibition prior to intervention results in improved outcomes and platelet inhibition during the procedure with glycoprotein IIb/IIIa inhibitors results in an improvement over heparin alone. In addition to platelet inhibition, direct thrombin inhibitors may offer further improvement by breaking the thrombin-platelet activation thrombus cycle.

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