TABLE 143-1 FEATURES OF GPIIB/IIIA ANTAGONISTS

Feature	Abciximab	Eptifibatide	Tirofiban
Description	Fab fragment of humanized mouse monoclonal antibody	Cyclical KGD-containing heptapeptide	Nonpeptidic RGD mimetic
Specific for Gp IIb/IIIa	No	Yes	Yes
Plasma half-life	Short (min)	Long (2.5 h)	Long (2.0 h)
Platelet-bound half-life	Long (days)	Short (s)	Short (s)
Renal clearance	No	Yes	Yes

a long half-life and can be detected on the surface of platelets for up to 2 weeks; eptifibatide and tirofiban have short half-lives.

Whereas eptifibatide and tirofiban are specific for Gp IIb/IIIa, abciximab also inhibits the closely related $\alpha_v\beta_3$ receptor, which binds vitronectin, and $\alpha_M\beta_2$, a leukocyte integrin. Inhibition of $\alpha_v\beta_3$ and $\alpha_M\beta_2$ may endow abciximab with anti-inflammatory and/or antiproliferative properties that extend beyond platelet inhibition.

Indications Abciximab and eptifibatide are used in patients undergoing percutaneous coronary interventions, particularly those who have not been pretreated with an ADP receptor antagonist. Tirofiban is used in high-risk patients with unstable angina. Eptifibatide also can be used for this indication.

Dosing All of the Gp IIb/IIIa antagonists are given as an IV bolus followed by an infusion. The recommended dose of abciximab is a bolus of 0.25 mg/kg followed by an infusion of 0.125 μg/kg per minute to a maximum of 10 μg/kg for 12 h. Eptifibatide is given as two 180 μg/kg boluses given 10 min apart, followed by an infusion of 2.0 μg/kg per minute for 18–24 h. Tirofiban is started at a rate of 0.4 μg/kg per minute for 30 min; the drug is then continued at a rate of 0.1 μg/kg per minute for up to 18 h. Because these agents are cleared by the kidneys, the doses of eptifibatide and tirofiban must be reduced in patients with renal insufficiency. Thus, the eptifibatide infusion is reduced to 1 μg/kg per minute in patients with a creatinine clearance below 50 mL/min, whereas the dose of tirofiban is cut in half for patients with a creatinine clearance below 30 mL/min.

Side Effects In addition to bleeding, thrombocytopenia is the most serious complication. Thrombocytopenia is immune-mediated and is caused by antibodies directed against neoantigens on Gp IIb/IIIa that are exposed upon antagonist binding. With abciximab, thrombocytopenia occurs in up to 5% of patients. Thrombocytopenia is severe in ~1% of these individuals. Thrombocytopenia is less common with the other two agents, occurring in ~1% of patients.

NEW ANTIPLATELET AGENTS

New agents in advanced stages of development include cangrelor, a parenteral, rapidly acting, reversible inhibitor of $P2Y_{12}$, and vorapaxar, an orally active inhibitor of protease-activated receptor 1 (PAR-1), the major thrombin receptor on platelets (Fig. 143-3).

Cangrelor An adenosine analogue, cangrelor binds reversibly to $P2Y_{12}$ and inhibits its activity. The drug has a half-life of 3–6 min and is given IV as a bolus followed by an infusion. When stopped, platelet function recovers within 60 min. A trial comparing cangrelor with placebo during percutaneous coronary interventions and a study comparing cangrelor with clopidogrel after such procedures revealed little or no advantage of cangrelor. A third trial compared cangrelor (given as an IV bolus of 30 μg/kg followed by an infusion of 4 μg/kg per minute for at least 2 h, or for the duration of the procedure, whichever was longer) with a loading dose of clopidogrel (300 or 600 mg) in 11,145 patients undergoing urgent or elective percutaneous coronary intervention. The rate of the primary efficacy endpoint, a composite of death, MI, ischemia-driven revascularization, and stent thrombosis, was 4.7% in the cangrelor group and 5.9% in the clopidogrel group ($p = .005$). The rates of severe bleeding, the primary safety endpoint, were 0.16% and 0.11% in the cangrelor and clopidogrel groups, respectively. Using the same efficacy endpoint, a prespecified meta-analysis of the three trials revealed a relative risk reduction of 19% with cangrelor compared with clopidogrel (3.8% and 4.7%, respectively) and a 40% reduction in stent thrombosis (0.5% and 0.8%, respectively) with no significant increase in serious bleeding. Based on these data, cangrelor is currently under regulatory review.

Vorapaxar An orally active PAR-1 antagonist, vorapaxar is slowly eliminated with a half-life of about 200 h. When compared with placebo in 12,944 patients with acute coronary syndrome without ST-segment elevation, vorapaxar failed to significantly reduce the primary efficacy endpoint, a composite of cardiovascular death, MI, stroke, recurrent ischemia requiring rehospitalization, and urgent coronary revascularization. Moreover, vorapaxar was associated with increased rates of bleeding, including intracranial bleeding.

In a second trial, vorapaxar was compared with placebo for secondary prevention in 26,449 patients with prior MI, ischemic stroke, or peripheral arterial disease. Overall, vorapaxar reduced the risk for cardiovascular death, MI, or stroke by 13%, but doubled the risk of intracranial bleeding. In the prespecified subgroup of 17,779 patients with prior MI, however, vorapaxar reduced the risk for cardiovascular death, MI, or stroke by 20% compared with placebo (from 9.7% to 8.1%, respectively). The rate of intracranial hemorrhage was higher with vorapaxar than with placebo (0.6% and 0.4%, respectively; $p = .076$) as was the rate of moderate or severe bleeding (3.4% and 2.1%, respectively; $P < 0.0001$). Based on these data, the drug is under consideration for regulatory approval in MI patients under the age of 75 years who have no history of stroke or transient ischemic attack and have a weight over 60 kg.

ANTICOAGULANTS

There are both parenteral and oral anticoagulants. The parenteral anticoagulants include heparin, low-molecular-weight heparin (LMWH), fondaparinux (a synthetic pentasaccharide), lepirudin, desirudin, bivalirudin, and argatroban. Currently available oral anticoagulants include warfarin; dabigatran etexilate, an oral thrombin inhibitor; and rivaroxaban and apixaban, oral factor Xa inhibitors. Edoxaban, a third oral factor Xa inhibitor, is undergoing regulatory review.

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 and is a polymer of alternating D-glucuronic acid and *N*-acetyl-D-glucosamine residues.

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. Antithrombin, the obligatory plasma cofactor for heparin, is a member of the serine protease inhibitor (serpin) superfamily. Synthesized in the liver and circulating in plasma at a concentration of 2.6 ± 0.4 μM, antithrombin acts as a suicide substrate for its target enzymes.

To activate antithrombin, heparin binds to the serpin via a unique pentasaccharide sequence that is found on one-third of the chains of commercial heparin (Fig. 143-5). Heparin chains without 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. 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