Figure 21.1 Summary of drugs used in treating dysfunctions of hemostasis.

IV. Platelet Aggregation Inhibitors

Platelet aggregation inhibitors decrease the formation of a platelet-rich clot or decrease the action of chemical signals that promote platelet aggregation (Figure 21.5). The platelet aggregation inhibitors described below inhibit cyclooxygenase-1 (COX-1), block GP IIb/IIIa, or block ADP receptors, thereby interfering with the signals that promote platelet aggregation. These agents are beneficial in the prevention and treatment of occlusive cardiovascular diseases, in the maintenance of vascular grafts and arterial patency, and as adjuncts to thrombin inhibitors or thrombolytic therapy in MI.

Medication	Adverse Effects	Drug Interactions	Monitoring Parameters
Oral Agents:			
Aspirin	Angioedema Bleeding Bronchospasm GI disturbances Reye syndrome SJS	Anticoagulants, P2Y12 inhibitors, NSAIDs—increased bleeding *cidofovir*—nephrotoxicity *probenecid*—decreased uricosuric effects	CBC LFT
Cilostazol	Bleeding GI disturbances Headache Peripheral edema SJS	Food (administer on empty stomach)	CBC
Clopidogrel	Bleeding SJS	Strong CYP2C19 inhibitors reduce antiplatelet effect (e.g., *omeprazole*)	CBC LFT
Dipyridamole	Bleeding Dizziness GI discomfort Rash	Salicylates—increased bleeding Thrombolytic agents—increased bleeding	None for oral administration
Prasugrel	Angioedema Bleeding Headache Hyperlipidemia Hypertension	Anticoagulants—increased bleeding Other antiplatelets—increased bleeding	CBC
Ticagrelor	Bleeding Dyspnea Headache Raised SCr	Strong CYP3A4 inhibitors (e.g., *ketoconazole*)—increased bleeding Strong CYP3A4 inducers (e.g., *rifampin*)—decreased efficacy	CBC LFT
Injectable Agents:			
Abciximab *Eptifibatide* *Tirofiban*	For all agents: Hypotension Nausea Vomiting Thrombocytopenia	For all agents: Increased bleeding: *Ginkgo biloba* Antiplatelets Salicylates SSRIs and SNRIs	For all agents: APTT clotting time H/H platelet count thrombin time

Figure 21.5 Summary of characteristics of platelet aggregation inhibitors. APTT = activated partial thromboplastin time, CBC = complete blood count, GI = gastrointestinal, H/H = hemoglobin and hematocrit, LFT = liver function test, NSAID = nonsteroidal anti-inflammatory drug, SCr = serum creatinine, SJS = Stevens-Johnson Syndrome, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

Study Questions

Choose the ONE best answer.

21.1 Which of the $P2Y_{12}$ ADP receptor antagonists reversibly binds the receptor?

A. *Clopidogrel*
B. *Prasugrel*
C. *Ticagrelor*
D. *Ticlopidine*

Correct answer = C. Of the $P2Y_{12}$ ADP receptor antagonists listed, ticagrelor is the only one that reversibly binds the receptor. This is important when it comes to compliance. If a patient is not compliant, then the antiplatelet activity of ticagrelor stops when the drug is missed (since the platelets are not irreversibly inhibited as they would be with aspirin, clopidogrel, or prasugrel).

21.2 A 70-year-old woman is diagnosed with nonvalvular atrial fibrillation. Her past medical history is significant for chronic kidney disease, and her renal function is moderately diminished. Which anticoagulant for atrial fibrillation avoids the need for renal dose adjustment in this patient?

A. *Apixaban*
B. *Dabigatran*
C. *Rivaroxaban*
D. *Warfarin*

Correct answer = D. Warfarin does not require dosage adjustment in renal dysfunction. The INR is monitored and dosage adjustments are made on the basis of this information. All of the other agents are renally cleared to some extent and require dosage adjustments in renal dysfunction.

21.3 An 80-year-old man is taking *warfarin* indefinitely for the prevention of deep venous thrombosis. He is compliant, has a stable INR, and denies bleeding or bruising. He is diagnosed with a urinary tract infection and is prescribed *sulfamethoxazole/trimethoprim*. What are the expected effects on his *warfarin* therapy?

A. Decreased anticoagulant effect of *warfarin*
B. Increased anticoagulant effect of *warfarin*
C. Activation of platelet activity
D. No change in anticoagulation status

Correct answer = B. Sulfamethoxazole/trimethoprim has a significant drug interaction with warfarin, such that it inhibits warfarin metabolism. Therefore, sulfamethoxazole/trimethoprim will cause increased anticoagulant effects, and the patient will need to have his warfarin dose decreased and INR checked frequently while he is on this antibiotic.

21.4 A 47-year-old woman presents to the emergency room with severe bleeding. Upon evaluation of the medical record, you discover that she takes dabigatran for a history of multiple DVTs. What is the appropriate reversal agent to administer to the patient at this time?

A. *Protamine*
B. Vitamin K
C. *Idarucizumab*
D. A reversal agent does not exist for this medication

Correct answer = C. Idarucizumab is used to reverse bleeding caused by dabigatran. By binding to dabigatran and its metabolites, idarucizumab neutralizes anticoagulation. It would be important to monitor this patient for any signs of thrombosis due to reversal of her anticoagulation. Vitamin K is the antidote for warfarin, and protamine is the antidote for heparin.

21.5 Which must heparin bind to in order to exert its anticoagulant effect?

A. GP IIb/IIIa receptor
B. Thrombin
C. Antithrombin III
D. von Willebrand factor

Correct answer = C. Heparin binds to antithrombin III, causing a conformational change. This heparin/antithrombin III complex then inactivates thrombin and factor Xa.

21.6 Which is considered “fibrin selective” because it rapidly activates plasminogen that is bound to fibrin?

A. *Alteplase*
B. *Fondaparinux*
C. *Argatroban*
D. *Bivalirudin*

Correct answer = A. Alteplase has a low affinity for free plasminogen in the plasma, but it rapidly activates plasminogen that is bound to fibrin in a thrombus or a hemostatic plug. It has the advantage of lysing only fibrin, without unwanted degradation of other proteins (notably fibrinogen).

21.7 A 56-year-old man presents to the emergency room with complaints of swelling, redness, and pain in his right leg. The patient is diagnosed with acute DVT, and the provider wants to start an oral agent. Which drug is most appropriate for treatment of DVT in this patient?

A. *Rivaroxaban*
B. *Betrixaban*
C. *Enoxaparin*
D. *Clopidogrel*

Correct answer = A. Betrixaban is only approved for the prophylaxis of DVT and PE; it is not approved for the treatment of acute DVT. Enoxaparin is used for the treatment of DVT, but it is an injectable medication. Clopidogrel is an antiplatelet medication that is not appropriate for acute treatment of DVT.

21.8 Which is most appropriate for reversing the anticoagulant effects of heparin?

A. *Aminocaproic acid*
B. *Protamine sulfate*
C. *Vitamin* K_1
D. *Tranexamic acid*

Correct answer = B. Excessive bleeding may be managed by ceasing administration of *heparin* or by treating with *protamine sulfate*. Infused slowly, *protamine sulfate* combines ionically with *heparin* to form a stable, inactive complex. *Aminocaproic acid* and *tranexamic acid* are approved for the treatment of hemorrhage but do not specifically reverse the effects of *heparin* to stop bleeding. *Vitamin* K_1 is used to help reverse the effects of *warfarin*-induced bleeding.

21.9 A 62-year-old man taking warfarin for stroke prevention in atrial fibrillation presents to his primary care physician with an elevated INR of 10.5 without bleeding. He is instructed to hold his warfarin dose and given oral *vitamin* K_1. When would the effects of vitamin K on the INR most likely be noted in this patient?

A. 1 hour
B. 6 hours
C. 24 hours
D. 72 hours

Correct answer = C. *Vitamin* K_1 takes about 24 hours to see a reduction in the INR. This is due to the time required for the body to synthesize new coagulation factors.

21.10 A 58-year-old man receives intravenous alteplase treatment for acute stroke. Five minutes following completion of alteplase infusion, he develops angioedema. Which of the following drugs may have increased the risk of developing angioedema in this patient?

A. ACE inhibitor
B. GP IIb/IIIa receptor antagonist
C. Phosphodiesterase inhibitor
D. Thiazide diuretic

Correct answer = A. ACE inhibitors, aspirin, and *prasugrel* all have possible adverse effects including angioedema. In the setting of *alteplase* administration, ACE inhibitors have been associated with an increased risk of developing angioedema with concomitant use.