Reduction in HCY levels by supplementation with vitamin B_6, vitamin B_{12}, and folate is probably the most effective means of reducing modest HCY elevations, but such supplementation does not decrease atherothrombotic risk, regardless of the cause of hyperhomocysteinemia or the presence of the MTHFR polymorphism. Therefore, the origin of the connection between high HCY and thrombosis remains incomplete, and the search for associated factors that link HCY and hypercoagulability continues.

Role of Platelets in Atherothrombosis

Although EC-associated abnormalities clearly influence hemostasis, platelet activation and adhesion are also critical to the development of atherothrombosis, especially in patients with acute coronary syndrome or ischemic stroke. Antiplatelet therapies are the primary modalities for maintaining short- and long-term patency in arteries, especially after coronary revascularization. Antiplatelet therapy can be targeted against specific platelet functions, including cyclooxygenase-mediated formation of thromboxane A_2, interaction of adenosine diphosphate (ADP) with its platelet receptor, and binding of the glycoprotein IIb/IIIa complex (GPIIb/IIIa) to fibrinogen for aggregation (Table 52-1).

Aspirin has long been a mainstay in the treatment of myocardial infarction, angina, and stroke because of its irreversible inhibition of platelet cyclooxygenase, a process that blocks the release of thromboxane A_2. Aspirin effectively prevents platelet aggregation to weak physiologic agonists (see Table 51-5 in Chapter 51) over the lifetime of a platelet (7 to 10 days); however, aspirin poorly inhibits platelet stimulation by thrombin and other strong agonists such as collagen. Therefore, blockade of other platelet activation pathways is important for patients who are at risk for arterial thrombosis.

Some drugs used to treat stroke or coronary disease (i.e., clopidogrel and prasugrel) specifically block platelet P2RY12, the ADP receptor, from interaction with ADP in the clot milieu, thereby decreasing platelet recruitment by preventing locally released ADP from activating additional platelets. Clopidogrel is effective in combination with aspirin for preventing ischemic stroke and for blocking stent thrombosis after revascularization; however, a significant proportion (up to one third) of patients demonstrate functional platelet resistance to clopidogrel. Under such circumstances, clopidogrel is poorly metabolized to its active form because of the presence of polymorphisms in the cytochrome P-450 gene, *CYP2C19,* that cause loss of function.

TABLE 52-1 ANTIPLATELET THERAPIES

INHIBITORS OF CYCLOOXYGENASE	PHOSPHODIESTERASE INHIBITORS
Aspirin Nonaspirin NSAIDs (not COX2 selective)	Dipyridamole Prostacyclin
P2RY12 ANTAGONISTS	**GPIIB/IIIA BLOCKERS**
Prasugrel Ticagrelor Clopidogrel	Abciximab Integrilin Tirofiban

COX2, Cyclooxygenase 2; GPIIb/IIIa, glycoprotein IIb/IIIa complex; NSAIDs, nonsteroidal anti-inflammatory drugs.

The more potent inhibitor, prasugrel, is not affected by cytochrome P-450 genotypes, although nongenetic factors such as platelet turnover, absorption, and compliance also play important roles in response variability.

Antiplatelet therapy with aspirin and a P2RY12 inhibitor (clopidogrel, prasugrel, or ticagrelor) reduces the risk of stent thrombosis and subsequent cardiovascular events after percutaneous coronary intervention and should be administered for 12 months unless the patient is at high risk for bleeding. In acute coronary syndrome, prasugrel and ticagrelor further reduce cardiovascular ischemic events compared with clopidogrel, although they are associated with higher bleeding risk. This effect occurs because drug interactions and variant cytochrome genotypes do not significantly affect production of the active metabolites of prasugrel and ticagrelor; the result is greater and more rapid inhibition of P2RY12 receptor–mediated platelet aggregation in most patients.

A third avenue for blocking platelet activation targets GPIIb/IIIa, the primary platelet receptor for binding to fibrinogen and vWF. Abciximab, a modified monoclonal antibody, prevents GPIIb/IIIa from binding to fibrinogen and blocks platelet aggregation after angioplasty, stent placement, or pharmacologic thrombolysis. Abciximab has been shown to reduce the incidence of recurrent acute ischemic events after percutaneous coronary revascularization in patients with myocardial infarction or unstable angina, mainly by decreasing the incidence of platelet-mediated thrombosis within the infarct-related vessel during and after the procedure. Other GPIIb/IIIa blockers, including eptifibatide (Integrilin) and tirofiban (Aggrastat), interfere with the GPIIb/IIIa arginine-glycine-aspartate (RGD) binding sites; they are used acutely for parenteral administration in patients with acute coronary syndrome or to maintain coronary patency after percutaneous coronary intervention. Thrombocytopenia is an uncommon (<2%) complication of all the GPIIb/IIIa inhibitors; it is most likely related to exposure of neoepitopes on the receptor and immune-mediated platelet destruction. Clearance of the drug typically resolves the thrombocytopenia within 1 week. Platelet transfusion should be considered only if there is significant thrombocytopenic bleeding because of the association of this procedure with a high incidence of stent thrombosis after stent implantation.

Additional novel strategies for mediating platelet activity include inhibition of cyclic nucleotide phosphodiesterases (e.g., dipyridamole, cilostazol) and blockade of proteinase-activated receptor 1 (PAR-1). Phosphodiesterase inhibitors most likely have multiple mechanisms of action. They result in decreased signal transduction within platelets, which impairs their responsiveness. PAR-1 is one of two principal recognized targets for thrombin stimulation of platelets, the other being PAR-4. The potential benefit of adding phosphodiesterase or PAR-1 inhibitors to aspirin and/or clopidogrel (e.g., prevention of restenosis in atherothrombosis) is being evaluated.

Venous Thromboembolism: Inherited Risk Factors

The balance between thrombin formation and anticoagulant pathways has been extensively studied in patients with inherited deficiencies of naturally occurring anticoagulants (Table 52-2).