In patients with stable and unstable coronary disease and those undergoing coronary stenting, the activation of platelets plays a central role in the occurrence of major thrombotic events such as death, myocardial infarction and stent thrombosis. Antiplatelet therapy for primary and secondary prevention of thromboembolic events is a cornerstone for the management of these patients and for many years the cyclooxygenase-1 (COX-1) inhibitor aspirin and the second generation thienopyridine clopidogrel which targets the ADP P2Y12 receptor on platelets served as the main antiplatelet agents for these indications. Clopidogrel in particular is very efficient in reducing ischemic cardiovascular events but exposes patients to an increased risk of bleeding. Therefore the optimal dosage and duration of clopidogrel therapy is of utmost importance. Furthermore, platelet function studies have revealed that responsiveness to clopidogrel is not uniform and that a low response is linked to a higher incidence of thrombotic events. Causes are multifactorial and several genetic and non-genetic factors including patients’ co-morbidities and co-medications have been identified. As a result clopidogrel's long lasting monopole as the only antiplatelet agent in patients undergoing coronary stenting is currently challenged by the newer P2Y12 blockers such as prasugrel and ticagrelor, which provide a stronger and more consistent inhibition of platelets. In the setting of acute coronary syndromes, this more potent platelet inhibition led
to less thrombotic events with these newer agents, but at the cost of a higher bleeding risk. This review provides an overview of the indication, dosage and duration of clopidogrel therapy and discusses its role in light of the recent introduction of newer P2Y12 receptor antagonists, the combination with newer oral anticoagulants such as dabigatran, apixaban and rivaroxaban as well as the emerging use of platelet function testing in clinical practice.