Rupture of an atherosclerotic plaque exposes a thrombogenic matrix, which instantly triggers platelet tethering and activation. We here delineate the sequence of events during arterial thrombus formation and dissect the specific role of the various platelet receptors in this process. We also discuss the interplay of platelets with circulating immune cells, which support arterial thrombosis by fibrin formation in a process that involves extracellular nucleosomes. In the second part of this chapter we describe the role of platelets in atherosclerotic lesion formation. Platelets adhere to the dysfunctional endothelium early during atherogenesis. They contain a large machinery of proinflammatory molecules, which can be released upon their activation. This prepares the ground for subsequent leukocyte recruitment and infiltration, and boosts the inflammatory process of the arterial wall. Together, platelets play a critical role in both acute and chronic processes of the vascular wall, which makes them an attractive target for pharmacological strategies to treat arterial thrombosis and, potentially, also atheroprogression.