The introduction of percutaneous intervention represented a major milestone in the management of obstructive arterial disease. Restenosis following intervention has been a key limitation of this therapy and, despite availability of a variety of therapeutic options, remains a challenging clinical entity. The aim of this review is to summarize the extensive literature regarding prevention and management of restenosis following percutaneous intervention. While systemic pharmacological approaches to reduce restenosis have not yielded convincing long-term results, drug-eluting stents (DES) have proven very effective, though their undoubted efficacy seems to be achieved at the collateral cost of delayed healing of the stented segment. The optimal management of DES restenosis remains under investigation: treatment options include repeat DES, angioplasty, brachytherapy or drug-eluting balloon. A comprehensive overview of systemic and local drug delivery approaches for prevention and treatment of restenosis. Current approaches to prevent and treat restenosis are efficacious, but there remains some distance to be travelled before patients or physicians can be fully satisfied with available therapies.