Percutaneous coronary intervention (PCI) with stent implantation has revolutionized the treatment of obstructive coronary artery disease. However, the main limitation of this therapy is stent failure, which is usually caused by in-stent restenosis. The aim of this article is to critically review the literature on the prevention of in-stent restenosis focusing on drug compounds that have reached clinical testing. The pathophysiological response following PCI includes many possible targets for antirestenosis treatment. Most notable success is seen with sirolimus (and its analogs) and paclitaxel, both of which target vascular smooth muscular cell proliferation. In view of the systemic side effects of both drugs, the high efficacy of local drug delivery methods reduced enthusiasm for systemic therapy. Cilastazol has shown benefit in restenosis reduction particularly in patients at high risk for stent failure, though further study in broader populations is warranted. Probucol showed variable results, but local drug delivery in combination with sirolimus seems promising. A hypothesized independent antirestenotic effect of pioglitazone in patients with diabetes has not been clearly demonstrated. Initial encouraging results with tranilast have not been replicated in a recent large-scale randomized trial. Colchicine and prednisone have shown promising results but require further investigation in larger clinical trials.