Randomized, double-blind, placebo-controlled trial of oral sirolimus for restenosis prevention in patients with in-stent restenosis: the Oral Sirolimus to Inhibit Recurrent In-stent Stenosis (OSIRIS) trial.

BACKGROUND: Despite recent advances in interventional cardiology, including the introduction of drug-eluting stents for de novo coronary lesions, the treatment of in-stent restenosis (ISR) remains a challenging clinical issue. Given the efficacy of systemic sirolimus administration to prevent neointimal hyperplasia in animal models and to halt and even reverse the progression of allograft vasculopathy, the aim of the present double-blind, placebo-controlled study was to evaluate the efficacy of a 10-day oral sirolimus treatment with 2 different loading regimens for the prevention of recurrent restenosis in patients with ISR.

METHODS AND RESULTS: Three hundred symptomatic patients with ISR were randomly assigned to 1 of 3 treatment arms: placebo or usual-dose or high-dose sirolimus. Patients received a cumulative loading dose of 0, 8, or 24 mg of sirolimus 2 days before and the day of repeat intervention followed by maintenance therapy of 2 mg/d for 7 days. Angiographic restenosis at 6-month angiography was the primary end point of the study. Restenosis was significantly reduced from 42.2% to 38.6% and to 22.1% in the placebo, usual-dose, and high-dose sirolimus groups, respectively (P=0.005).
Similarly, the need for target vessel revascularization was reduced from 25.5% to 24.2% and to 15.2% in the placebo, usual-dose, and high-dose groups, respectively (P=0.08). The sirolimus blood concentration on the day of the procedure correlated significantly with the late lumen loss at follow-up (P<0.001). CONCLUSIONS: In patients with ISR, an oral adjunctive sirolimus treatment with an intensified loading regimen before coronary intervention resulted in a significant improvement in the angiographic parameters of restenosis.