Restenosis in clinical practice
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Chapter 9

Primary Stenting of Occluded Native Coronary Arteries II:

Rationale and design of the PRISON II study

A randomized comparison of bare metal stent implantation with sirolimus-eluting stent implantation for the treatment of chronic total coronary occlusions

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ABSTRACT

Primary intracoronary stent placement after successfully crossing chronic total occlusions (CTO) decreases the high restenosis rate at long-term follow-up compared with conventional balloon angioplasty. Several studies have shown the efficacy of sirolimus-eluting stents in selected groups of patients. Whether sirolimus-eluting stents are superior to bare metal stents in CTO is unknown. In this prospective, randomized trial, bare metal stent implantation will be compared with sirolimus-eluting stent implantation for the treatment of CTO. A total of 200 patients will be followed for 12 months with angiographic follow-up at 6 months. Quantitative coronary analysis will be performed by an independent core lab. The primary end-point is the binary angiographic restenosis and re-occlusion rate.
INTRODUCTION

Since data from the two landmark studies, the BENESTENT and STRESS studies\textsuperscript{1,2}, showed that coronary stenting significantly decreases restenosis as compared with conventional balloon angioplasty, this treatment modality has shown to be superior in an increasing number of indications.\textsuperscript{1,2} Percutaneous coronary intervention (PCI) of chronic total occlusions (CTO) however is still limited by high restenosis rates. Although coronary stenting using bare metal stents significantly decreases restenosis in CTO, restenosis rates still reach 32-55%.\textsuperscript{3-8} In 200 patients with CTO randomized in the PRISON I study we demonstrated a restenosis rate of 22% after bare metal stent implantation as compared with 33% after conventional balloon angioplasty.\textsuperscript{9} During the past few years, sirolimus (rapamycin), a cytostatic macrocyclic lactone with anti-inflammatory and antiproliferative properties\textsuperscript{10-12}, delivered from a polymer-encapsulated stent was shown to almost eliminate the risk of restenosis in selected groups of patients.\textsuperscript{13-16}

In this study we will investigate the results of sirolimus-eluting stent implantation as compared with bare metal stent implantation in CTO.

METHODS

Patients

The PRImary Stenting of Occluded Native coronary arteries II (PRISON II) study is a randomized, two-center trial in which 200 patients will be recruited. We will investigate the effect of a bare metal stent (Bx VELOCITY\textsuperscript{TM})(Cordis corporation, Johnson&Johnson) versus a sirolimus-eluting stent (Cypher\textsuperscript{TM}) in chronic coronary occlusions. The bare metal stent and the sirolimus-eluting stent have the same design. Patients are included if the estimated duration of the chronic total occlusion is at least 2 weeks with evidence of ischemia related to the occluded coronary artery (signs of ischemia found during an abnormal exercise test, defined as ST depression of at least 1.0 mm that is horizontal or down-sloping or upsloping ST depression of at least 2.0 mm or signs of ischemia found during nuclear imaging with exercise, dobutamine or adenosine). Patients are excluded if the lesion can not be crossed or if the use of aspirin and clopidogrel is prohibited. The study is conducted according to the principles of the Declaration of Helsinki, and all patients have to give written informed consent before they undergo the procedure.

Hypertension is defined as a systolic tension higher than 140 mmHg and/or a diastolic tension higher than 90 mmHg or use of anti-hypertensive drugs. Diabetes mellitus is defined as fasting venous glucose concentrations $\geq$ 7.8 mmol/L (140.5 mg/dL) or use of glucose lowering drugs. Hypercholesterolemia is defined as a fasting plasma cholesterol level higher than 5.0 mmol/L (193 mg/dL) or use of cholesterol lowering drugs.

Angiographic definitions

Chronic total coronary artery occlusion is defined by the absence of antegrade flow of contrast distal to the occlusion (flow grade 0 according to the Thrombolysis and Myocardial Infarction [TIMI] score) or only minimal flow of contrast distal to the occluded vessel (TIMI flow I).\textsuperscript{17} The duration of the chronic occlusion has to be at least 2 weeks and is estimated by clinical information, sequential angiographic information, or both.
The estimated length of the occlusion is measured from the point of the chronic occlusion to the most proximal point of the distal vessel, which is visualized by collateral filling with contrast. The total coronary analysis segment is defined as the stented segment including the margins 5 mm distal and proximal to the stents.

**Angioplasty procedure**

Percutaneous coronary intervention is performed from either the femoral artery or radial artery approach with standard recanalization and stent implantation techniques. The major goal is to achieve a residual luminal diameter stenosis <30% on visual assessment. Randomization is performed after crossing the lesion, but before initial dilatation. Patients are randomized by a telephone allocation service, which was provided with the randomization list before recruitment of the first patient. Patients are equally assigned to either the conventional bare metal stent group or the sirolimus-eluting stent group. Both patient and treating physician are blinded for allocation. Poststent dilatation is performed with high inflation pressures in all patients. At the beginning of the procedure patients receive a single dose of 10,000 U heparin. All patients receive aspirin and clopidogrel before the procedure. Clopidogrel will be continued for 1 year and aspirin is given lifelong.

**Quantitative coronary analysis**

The angiograms will be analyzed by an independent core angiography laboratory (Research&Development department, cardiology department, St. Antonius Hospital, Nieuwegein, The Netherlands). The observers are not provided with the clinical information of the patients. Before angiography 500 µg nitroglycerine is given intracoronary. The guiding catheter is used as the calibration standard. All lesions are assessed in at least two orthogonal views and the projection showing the smallest diameter is used for quantitative coronary angiography analysis, and views with the least foreshortening are used for measuring the length of the occlusion. In disease-free proximal segments the reference diameter is measured. Cineangiograms will be obtained before, immediately after and at 6 months, using the same views. Any coronary angiography performed within 3 months after the initial procedure will be considered unscheduled. When an unscheduled angiography is followed by target lesion revascularization no further angiograms are needed. If no target lesion revascularization takes place, repeat angiography at 6 months still will be required. If the angiography takes place after 3 months, 6 months angiographic assessment is not mandatory.

The early gain is defined as the difference between the minimal luminal diameter (MLD) after intervention and the diameter before intervention. Late loss is defined as the subsequent decrease in MLD of the treated artery at the 6-month follow-up angiography. The loss index is defined as the late loss divided by the early gain.

**Long-term follow-up**

Clinical follow-up will be performed at 6 months, 1 year, and 5 years. Recurrent angina, a positive exercise test, or abnormal nuclear imaging are considered as clinical signs of restenosis. Follow-up angiography will be performed earlier if there are clinical signs of restenosis and if indicated, followed by target lesion revascularization. Death, myocardial infarction (MI, defined as the presence of new significant Q waves or an elevation of creatine kinase or its MB isoenzyme to at least two times the upper limit), occurrence of angina (Canadian Cardiovascular Society [CCS] class III or IV), or target lesion revascularization (TLR, defined as percutaneous or surgical revascularization of the target lesion after the initial procedure) will be recorded as major adverse clinical events (MACE).
Restenosis and reocclusion

Angiographic in-stent restenosis at follow-up is defined as > 50% residual diameter stenosis in the stent. Edge restenosis at follow-up is defined as >50% residual diameter stenosis located at the proximal or distal edge. Reocclusion is defined as a recurrent total occlusion at the previous angioplasty site.

End-points

The primary end-point is the binary angiographic restenosis/re-occlusion rate at 6-month follow-up as assessed by an independent core lab. Pre-specified secondary endpoints are: in-stent/in-segment MLD and diameter stenosis at 6 months follow-up as assessed by an independent core laboratory and rates of TLR, MI, stroke and death until the 12 months clinical follow-up.

Statistical analysis

Assuming the restenosis rate in the conventional PCI group to be 22% and projecting the restenosis rate in the sirolimus-eluting stent group to be between 5% and 7%, furthermore setting the alpha level at 5% (two-sided) and the power to be at least 80%, this study needs to evaluate 93 patients in both study groups. Allowing for a low dropout rate, comparable to the PRISON I study\(^9\), 100 patients in each group is the target sample size.

The primary endpoint is the angiographic restenosis/reocclusion rate at 6 months follow-up. The comparison between the two groups will be assessed by means of Fisher’s exact test for a 2×2 table. The in-segment and in-stent percent diameter stenosis, MLD, and late loss will be compared by means of the Student’s t-test. Additional multivariate analyses will only be performed as hypothesis generating method.

CONCLUSIONS

Despite bare metal coronary stents, chronic total occlusions continue to pose a problem both to the interventionalist and the patient due to the high rate of restenosis. The PRISON II study will allow determination of the value of sirolimus-eluting stents in patients with chronic total occlusions.
References