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Testing prospectively the effectiveness and safety of paclitaxel-eluting stents in over 1000 very high-risk patients
Design, baseline characteristics, procedural data and in-hospital outcomes of the multicenter Taxus in Real-life Usage Evaluation (TRUE) Study

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Abstract

Background: Paclitaxel-eluting stents (PES) have been proved effective in randomized trials enrolling highly selected patients. Yet, given the uncertainty concerning results of PES implantation in very high-risk patients and lesions, we designed a prospective multicenter registry, the Taxus in Real-life Usage Evaluation (TRUE) Study.

Study design, patient characteristics and in-hospital outcomes: Consecutive patients undergoing PES implantation were enrolled provided that the target lesion treated with PES was an unprotected left main (ULM), a true bifurcation, a chronic total occlusion (CTO), a long lesion (>28 mm), located in a small vessel (<2.75 mm), or the patient had diabetes mellitus. Clinical events will be adjudicated at 1, 7 and 12 months, with 4- to 8-month angiographic follow-up. The primary end-point will be the 7-month occurrence of major adverse cardiovascular events (MACE, i.e. the composite of cardiac death, non-fatal myocardial infarction [MI], coronary artery bypass grafting [CABG] and percutaneous target vessel revascularization [TVR]).

To date, patient enrolment has been completed reaching the target of 1065 subjects. These included 322 (30.2%) diabetics, 115 (10.8%) subjects undergoing PES implantation for ULM, 229 (21.5%) in a bifurcation, 191 (17.9%) in a CTO, 430 (40.4%) in a small vessel, and 289 (27.1%) in a long lesion. An average of 1.5±0.6 vessels and 2.0±1.0 lesions were treated per patient, with 2.0±1.2 PES implanted per patient, and a 46±30 mm total PES length per patient. In-hospital MACE occurred in 39 (3.7%) patients, with 2 (0.2%) cardiac deaths, 32 (3.0%) MI, 5 (0.5%) TVR, no CABG, and 4 (0.4%) acute stent thromboses.

Implications: Despite the availability of randomized trials, only carefully designed and prospective registries can provide timely and accurate assessment of the risk–benefit profile of PES in very high-risk patients. Indeed, the TRUE Study, including as much as 115 ULM and 229 bifurcation interventions, should give important insights into the outcome of PES in such an unprecedented and challenging context.

Keywords: Coronary artery disease; Drug-eluting stent; Paclitaxel-eluting stent; Restenosis; Study design

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1. Introduction

Drug-eluting stents (DES) have been proved effective in comparison to bare-metal stents (BMS) in reducing restenosis in selected patients and lesions, without increasing in-hospital adverse event or long-term death or myocardial infarction rates [1]. Specifically, a wealth of data have supported the international approval of both sirolimus-eluting stents (Cypher, Cordis, Miami, FL, USA) and paclitaxel-eluting stents (PES, Taxus, Boston Scientific, Natick, MA, USA), and, indeed, since the publication of the first feasibility study in humans in January of 2003, PES have entered the mainstream of interventional cardiology [2–5].

Most recently, results of PES implantation in more challenging lesions and patients have been presented, including the results of the TAXUS V and VI studies [6,7]. Despite the encouraging results of these trials, and while awaiting for the ongoing SYNTAX trial of coronary artery bypass surgery (CABG) vs. PES in patients with triple vessel or unprotected left main (ULM) disease, the interventional cardiology community is however in the difficult situation of either avoiding the potentially beneficial implantation of a PES in a patient not strictly fulfilling the stringent selection criteria of the available randomized trials, or deciding for implanting a PES despite the lack of a sound evidence base. In this context, interventionalists have to rely on muticenter registries and non-experimental studies [8,9], notwithstanding their inherent limitations [10]. Registries can provide the opportunity to test the risk–benefit ratio of PES in very high-risk or complex lesions unlikely to be the object of randomized comparison with BMS, such as ULM, chronic total occlusions (CTO), bifurcation lesions, or safenous vein grafts (SVG) [11–14]. Indeed, results of BMS in such complex settings have been largely disappointing, with mid-term major adverse cardiovascular events (MACE) rates respectively of 35% in ULM [11,12], and CTO [15], and ranging between 20% and 30% for in bifurcation lesions [16].

2. Rationale

Given the above premises, and especially the suboptimal results achieved by BMS in high-risk patients and lesions, we have designed and are currently conducting a multicenter, prospective clinical study enrolling high-risk patients undergoing PES implantation in 7 European tertiary care centers, with the aim of appraising the safety and efficacy of PES in subjects with ULM, CTO, true bifurcation lesions, long lesions, small vessel disease, or medically treated diabetes mellitus. In light of the large patient sample (over 1000), mandatory angiographic follow-up and systematic core lab quantitative coronary angiographic analysis, the Taxus in Real-life Usage Evaluation (TRUE) Study should provide important insights on the early to long-term results of PES in such challenging patients and lesions.

3. Patient selection

Consecutive patients undergoing PES implantation at participating centers were enrolled, provided that they could give written informed consent and were willing to undergo follow-up. Patients were included if at least 1 of the following criteria was present: 1) medically-treated diabetes mellitus, 2) planned ULM intervention, 3) planned bifurcation intervention (i.e. with a lesion located on a bifurcation and for which the operator performed dilatation or stent implantation on the side branch [thus with a reference vessel diameter >2.25 mm by visual estimate]), 4) small coronary artery disease (i.e. lesion with a reference vessel diameter [RVD] <2.75 mm by visual estimate), 5) CTO (totally occluded vessel known to be occluded for >1 month or for an unknown time period), or 6) long lesion (i.e. lesion with a length >28 mm by visual estimate). Exclusion criteria were: ongoing (<24 h) ST-elevation acute myocardial infarction, impossibility to assume or continue combined antiplatelet therapy (aspirin plus ticlopidine or clopidogrel) for >8 months following PES implantation, allergy to paclitaxel, and absence of written informed consent.

4. Procedure

Coronary angioplasty and PES implantation were performed according to the practice of fully covering the diseased segment [3,17]. At the start of the procedure, a bolus of heparin was recommended at a dosage of 70–100 IU/kg to achieve an activated clotting time >250 s. Enoxaparin, bivalirudin and/or glycoprotein IIb/IIIa inhibitors could be nonetheless administered at the operator's discretion. Patients were asked to start combined antiplatelet therapy with aspirin (>100 mg QD) and ticlopidine 250 mg BID or clopidogrel 75 mg QD >3 days before the procedure and to continue for >8 months. A preprocedural loading dose of >300 mg clopidogrel was recommended to those not previously taking thienopyridines.

No specific suggestions were made for ad hoc stenting techniques or ancillary devices, and thus direct stenting, rotational atherectomy, directional atherectomy, cutting balloon angioplasty and intravascular ultrasound were all allowed at the operator's discretion. In case of bifurcation treatment with provisional or T-stenting, final kissing balloon inflation was nonetheless strongly recommended [13].

All patients were also evaluated with standard pre-procedure and post-procedure ECG, and blood draws for creatine kinase (CK), CK-MB and cardiac troponin at 6 and 12 h post-procedure and, if elevated, until normalization.

5. Clinical and angiographic follow-up

Clinical follow-up was scheduled for all patients at discharge, and at 1, 6, and 12 months. Angiographic