PCI of complex coronary lesions, new stent technologies, and clinical outcomes
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Design and rationale of the TRI-stent Adjudication Study (TRIAS) Program

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Abstract

**Background** In the treatment of coronary artery disease, a “pro-healing” approach for prevention of in-stent restenosis and late stent thrombosis is intuitively favored over the use of cytotoxic or cytostatic drugs released from a drug-eluting stent (DES). Promoting accelerated endothelial coverage of the stent surface, the endothelial progenitor cell capturing stent (ECS) has shown its safety and efficacy in the HEALING observational studies; however, randomized trials evaluating the device are lacking.

**Methods** The multicenter, randomized, controlled, 2-armed TRIAS Program aims to include a total of 2560 patients. In the TRIAS Low Risk trial, a total of 1300 patients with lesions carrying a low risk of restenosis are randomized between the ECS and a bare metal stent, assuming superiority in the incidence of target lesion failure (TLF) at 1 year. In the TRIAS High Risk trial, 1260 patients with lesions carrying a high risk of restenosis are randomized, assuming the noninferiority in TLF at 1 year of the ECS as compared to DES. TLF is defined as the composite of cardiac death, myocardial infarction and clinically driven target lesion repeat revascularization. In addition, the duration of clinical follow-up is extended to 5 years to capture late events. Angiographic follow-up at 13 months is performed as part of the TRIAS Program ancillary study.

**Implication** The results of the TRIAS Program will provide information on a relevant patient population with coronary artery lesions, comprising the full spectrum of low risk and high risk of restenosis treated with a novel stent technology in a randomized, controlled manner. (TRIAS Low Risk trial: ISRCTN 47701105 and TRIAS High Risk trial: ISRCTN 74297220)
Introduction

The introduction of drug-eluting stents (DES) has significantly reduced the rate of clinically driven repeat target lesion revascularization (TLR) as compared to bare metal stents (BMS) in the treatment of symptomatic coronary artery disease.1-5 Drug-eluting stents release cytotoxic or cytostatic drugs locally to reduce the proliferation of vascular smooth muscle cells that give rise to neointimal hyperplasia causing in-stent-restenosis. By their nature, antiproliferative drugs seriously impede the natural healing response of the vessel wall, by which the stent struts are covered with a lining of normal, functional endothelium.6,7 This absence of healing may lead to an increased incidence of late and very late stent thrombosis and necessitates prolonged dual antiplatelet therapy. In addition, absence of vascular healing results in an inappropriate or impaired vasomotor response, and potentially late neointimal catch-up at long term follow-up.8,9

The bioengineered Genous endothelial progenitor cell capturing stent (OrbusNeich Medical Technologies Inc, Fort Lauderdale, FL) with its stainless steel platform is coated with an abluminal polysaccharide matrix and covalently coupled monoclonal murine antihuman CD34+ antibodies. These anti-CD34+ antibodies are able to bind bone marrow-derived circulating endothelial progenitor cells (EPCs) from the peripheral blood, and it is hypothesized that these EPCs differentiate into a functional endothelial layer after immobilization. Furthermore, it is hypothesized that after vascular injury caused by stent placement, the establishment of this layer will prevent neointimal proliferation and thrombus formation.10,11

The safety and efficacy of the EPC capturing stent (ECS) in clinically stable patients with a single, noncomplex, de novo lesion was shown in the HEALING-FIM and HEALING II studies.12-14 However, both studies were performed in a nonrandomized setting. In addition, at the time of writing the TRIAS Program study design, randomized trials evaluating the ECS in patients with complex lesions were lacking. In the multicenter randomized, 2-armed TRIAS Program, the treatment modality is guided on the risk of restenosis a lesion or patient is carrying: (1) the TRIAS Low Risk (LR) study comparing the ECS with the BMS in patients with lesions carrying a low risk of restenosis and (2) the TRIAS High Risk (HR) study comparing the ECS with DES in patients with lesions carrying a high risk of restenosis.

Methods

For the sake of legibility, the specifics of the TRIAS LR trial and TRIAS HR trial are discussed separately. Common aspects of both study arms, such as the informed consent procedure, randomization process, obtaining the clinical follow-up and the definition of the study endpoints are similar for both trials and will be discussed hereafter. The study design flow chart is shown in figure 1.
Figure 1. TRIAS Program study design flow chart.

1) TRIAS LR

Study objectives

The primary objective of the TRIAS LR trial is to demonstrate superiority of the ECS when compared to a BMS to prevent target lesion failure (TLF) within 1 year in patients undergoing a percutaneous coronary intervention (PCI) for de novo, coronary artery lesions with an anticipated low risk of restenosis.

Patient selection

Patients selected for elective PCI are candidates for enrollment when all lesions to be treated, meet all 4 criteria: (1) a lesion in a coronary artery with a reference vessel diameter >2.8 mm by visual estimation, (2) a coronary artery stenosis with a length <20 mm by visual estimation, (3) a coronary artery lesion with a TIMI flow ≥1 by visual estimation, and (4)
coronary lesions in nondiabetic patients. The principal exclusion criteria for the TRIAS LR trial are listed in Table I.

Table I Exclusion criteria TRIAS Program

The following general exclusion criteria apply for both studies:

1. Younger than 18 years of age
2. Any target lesion located in the left main coronary artery
3. Any target lesion with involvement of a side branch, which is equal to or greater than 2.0 mm in diameter by visual estimation
4. Any restenotic target lesion
5. Any target lesion in an arterial or saphenous vein graft or distal to a diseased arterial or saphenous vein graft
6. Urgent need for revascularization
7. ST Elevation Myocardial Infarction within the past six weeks
8. Ventricular tachyarrhythmias within the past week
9. Known renal insufficiency (e.g. serum creatinin level of more than 200 μgram/L)
10. Platelet count of less than 100,000 cells/ mm3 or more than 700,000 cells/ mm3, a WBC of less than 3,000 cells/ mm3, or documented or suspected liver disease (including laboratory evidence of hepatitis)
11. History of a bleeding diathesis, or evidence of active abnormal bleeding within 30 days of randomization
12. History of a hemorrhagic stroke at any time, or stroke or transient ischemic accident (TIA) of any etiology within 30 days of randomization
13. Previous or scheduled chemotherapy or radiotherapy within 30 days prior or after the procedure
14. On immune-suppression therapy or with known immunosuppressive or autoimmune disease (e.g. human immunodeficiency virus, systemic lupus erythematosus etc.)
15. Severe hypertension (SBP > 180 mmHg or DBP over 100 mmHg, after treatment)
16. Contraindication for treatment with the Genous™ EPC capturing stent, such as previous administration of murine therapeutic antibodies and exhibition of sensitization through the production of Human Anti-Murine Antibodies.
17. Contraindication(s) for treatment with the DES
18. Known hypersensitivity or contraindication to aspirin, heparin or clopidogrel.
19. Elective surgery, planned within the first 6 months after the procedure that requires discontinuing either aspirin or clopidogrel
20. Previous heart transplant or any other organ transplant
21. Previous participation in this trial
22. Circumstances that prevent follow-up (no permanent home or address, transient, etc.)
23. Women who are pregnant or who are of childbearing potential who do not use adequate contraception.

Specific TRIAS LR exclusion criteria:

24. Chronic, totally occluded target lesion
25. Diabetic patients
26. Target lesion with an indication for treatment with a drug-eluting stent
Treatment
In the TRIAS LR trial, patients are randomly assigned to one of the following treatment strategies: (1) treatment with the ECS or (2) treatment with a BMS type at the discretion of the operator. All target lesions must be treated according to the randomized treatment assignment. All lesions treated are used for the assessment of TLF and are used for quantitative coronary angiography (QCA) analysis.

Before and after the index procedure, all patients receive aspirin 75 to 100 mg daily and clopidogrel, a loading dose of 300 mg prior to the procedure and 75 mg daily for at least 1 month.

Statistical analysis
Analysis is based on the principle of intention to treat. In the TRIAS LR trial, sample size calculations were based on a null hypothesis of superiority of the primary efficacy endpoint at 1 year. With 2 x 600 analyzable patients, the trial has 90% power to detect superiority of the ECS with a 1-sided alpha of 5%. The calculation assumes a TLF rate of 10% under bare metal stenting and of 5% under EPC capturing stenting. To compensate for an attrition of 5%, 2 x 630 patients are entered into the trial. Secondary endpoints, listed in Table II, will be compared using the $\chi^2$ test or Fisher mid-P test, depending on the event rate, assuming a 0.05 level of significance. Differences in Kaplan-Meier plots of cardiac death, TLF, TLR, and target vessel revascularization (TVR) will be assessed using log-ranking tests.

2) TRIAS HR

Study objectives
The primary objective of the TRIAS HR trial is to demonstrate noninferiority of the ECS when compared to a DES to prevent TLF within 1 year in patients undergoing a PCI for de novo coronary artery lesions with an anticipated high risk of restenosis.

Patient selection
Patients selected for elective PCI are candidates for enrollment in the TRIAS HR trial when at least one target lesion has been identified as carrying a high risk of restenosis. A high-risk target lesion is identified when $\geq$ 1 of the following criteria are met: (1) a lesion in a coronary artery with a reference vessel diameter of $\leq$ 2.8 mm by visual estimation, (2) a coronary artery stenosis with a length of $\geq$ 20 mm by visual estimation, (3) a chronic coronary artery occlusion, or (4) any lesion in a diabetic patient. The principal exclusion criteria for the TRIAS HR trial are listed in Table I.
Table II Secondary endpoints TRIAS LR and TRIAS HR

The secondary end points for both trials are:

- **Target lesion failure** within two, three, four, or five years
- **Cardiac death or myocardial infarction** within one, two, three, four, or five years
  - **Stent thrombosis** within one, two, three, four, or five years
- **Target lesion revascularization** within one, two, three, four, or five years
- **Target vessel revascularization** within one, two, three, four, or five years

### Treatment

Patients are randomly assigned to one of the following treatment strategies: (1) treatment with the ECS or (2) treatment with a DES. The following DES are allowed to use in the TRIAS HR trial: the Taxus Paclitaxel-eluting stent (PES; Boston Scientific, Natick, MA), the Cypher Sirolimus-eluting stent (Cordis Corp, Miami Lakes, FL), the XIENCE V Everolimus-eluting stent (Abbott Vascular, Santa Clara, CA), and the Endeavor Zotarolimus-eluting stent (Medtronic, Inc, Minneapolis, MN). The choice of any of these 4 DES is at the discretion of the operator. All high-risk target lesions must be treated according to the randomized treatment assignment, and in case of DES placement, the same type must be used. In the TRIAS HR trial, low-risk lesions, if present, may be treated according to the treatment assignment or with a BMS. All treated high-risk lesions are used for the assessment of TLF and are used for QCA analysis.

Before and after the index procedure, all patients receive aspirin 75-100 mg daily and clopidogrel, a loading dose of 300 mg prior to the procedure and 75 mg daily for at least 1 month after receiving an ECS and at least 6 months after receiving a DES.

### Statistical analysis

In the TRIAS HR trial, sample size calculations were based on a null hypothesis of noninferiority of the primary efficacy endpoint at 1 year. With 2 x 620 analyzable patients, the trial has 90% power to detect noninferiority of the ECS with a 1-sided alpha of 5%. The calculation assumes equal target lesion rates of 10%, with a margin of noninferiority of 1.5 for the relative risk. To compensate for an attrition of 5%, 2 x 650 patients are entered into the trial. Secondary endpoints, listed in Table II, will be compared using the $\chi^2$ test or Fisher exact test, depending on the event rate, assuming a 0.05 level of significance. Differences in Kaplan-Meier plots of cardiac death, TLF, TLR, and target vessel revascularization (TVR) will be assessed using log-ranking tests.
3) Common procedures and study aspects of TRIAS LR and TRIAS HR

Informed consent procedure and randomization

In the TRIAS Program, written informed consent is obtained before the index procedure. Patients are randomized after the angiographic inclusion and exclusion criteria have been verified during the initial angiogram and the anticipated risk of restenosis and herewith eligibility for participation in the LR or HR arm of TRIAS is established. Before the actual randomization takes place, all low- and/or high-risk target lesions are identified as such. The patients are randomized via an electronic program accessible by entering the randomization website (www.triasrandomization.org). For each participating medical center, randomization blocks are created with randomly chosen block sizes of 1, 2, 3, or 4.

Follow-up

All patients are contacted for clinical follow-up at 1 and 6 months and at 1, 2, 3, 4, and 5 years after randomization either by telephone contact or planned visit to the clinic. The clinical, angiographic, and procedural characteristics and follow-up information will be entered in an electronic case report form. Patients are monitored for their anginal status, current medication, adverse cardiovascular events (repeat revascularization, myocardial infarction (MI), stent thrombosis, cardiovascular hospitalization, major extra-cranial bleeding, and stroke) and all-cause mortality. When a cardiovascular event is reported, review of hospital records, chart review, telephone contact with the referring cardiologists and/or the patient’s general practitioner are used to complete information. Furthermore, patients are evaluated for the development of angina pectoris according to the Canadian Cardiovascular Society Classification of stable angina or Braunwald Classification of unstable angina.

Endpoint definition and interim analysis

The primary efficacy endpoint of both the TRIAS LR and TRIAS HR trial is TLF within 1 year, defined as the composite of cardiac death, MI (unless documented to unequivocally arise from a nontreated coronary artery) and clinically driven repeat revascularization of any of the treated target lesions. The secondary endpoints of both studies are listed in Table II. The main long-term safety endpoint of both trials is defined as cardiac death or MI within 5 years of randomization. All endpoint definitions are in accordance with the Academic Research Consortium. Serious and unanticipated device-related and treatment-related adverse events are reported to the Data and Safety Monitoring Board (DSMB) in order to review treatment monitoring reports periodically for evidence of harm. After 50% of the patients are enrolled in TRIAS LR or TRIAS HR trial an interim assessment will be performed on both trials by the DSMB regarding the efficacy of the trial and/or safety of the patients. All study endpoints are adjudicated by an independent clinical event committee for the duration of the study, with members blinded to the assigned stent.
Current status

All 31 participating centers and their representatives are listed in appendix A. Recruitment has commenced in July 2007 and is expected to be completed in December 2009. Analyses and reporting is expected to be completed by January 2015.

Angiographic substudy of the TRIAS Program

In a subset of 300 patients enrolled in the TRIAS LR trial and 300 patients in the TRIAS HR trial repeat angiography will be performed between 13 and 15 months. The primary endpoint is in-stent late loss as assessed by QCA at follow-up angiography. All lesions treated at baseline will count for endpoint assessment; with the exception of the treated lesions at baseline that carry a low risk of restenosis in the TRIAS HR patients. Baseline and follow-up coronary angiograms will be analyzed at a QCA core laboratory.

Endothelial Progenitor Cell analysis substudy of the TRIAS Program

Endothelial progenitor cell analysis will be performed in a subset of 100 consecutive patients enrolled in the TRIAS Program at the Academic Medical Center, University of Amsterdam. CD34-positive cells and EPCs will be quantified using flow cytometry technique from a 20-mL EDTA blood sample that will be taken pre-procedural. Quantitative fluorescence analysis is performed using a FACS-CANTO flow cytometer and analyzed with FACS Diva software (BD Biosciences, San Jose, CA). Cells expressing CD34, CD133 and kinase insert domain receptor are counted as EPCs. Functional assessment is defined by the ability of EPCs to expand and form colonies in culture. The colony-forming units assay will be performed using the method originally described by Hill et al.16

For the sake of reproducibility and logistics, this substudy will only be performed in the Academic Medical Center.

Discussion

The TRIAS Program is an investigator initiated, multicenter, international, randomized trial evaluating the performance of the ECS in clinically stable patients with de novo coronary artery lesions. We designed 2 parallel studies based on the following considerations at the time of writing: (1) concerns about the safety of DES were addressed, in particular with respect to delayed endothelialization, chronic inflammatory reaction, and late stent thrombosis17-20; (2) implementation of DES requires long-term dual antiplatelet therapy; and (3) the use of DES might be less cost-effective than BMS in patients with lesions carrying a low risk of restenosis.21 Early observational studies could not assess the superiority in clinical outcome of DES over BMS in noncomplex coronary artery lesions.22-27 In line, the current European Society of Cardiology guidelines for PCI indicate that DES are recommended for patients with symptomatic coronary artery disease, in whom the target coronary artery is <3 mm in diameter or the lesion >15 mm in length.28 Therefore, in patients with all lesions
carrying a low risk of restenosis, a BMS serves as the control device, mimicking the preferred treatment for this subset of patients in daily practice. In patients with lesions carrying a high risk of restenosis, a significant reduction in repeat revascularization was observed after DES placement over BMS placement. Therefore, in patients with lesions carrying a high risk of restenosis, a DES serves as the control device. All 4 Conformité Européenne approved DES can be used in order to increase the number of participating hospitals using only a particular DES type, and thereby keeping up enrollment numbers.

In previous stent studies, concerns have risen about the use of protocol-driven follow-up angiography and its impact on revascularization rates that could be significantly increased due to the oculostenotic reflex, yielding rates which may not reflect ‘real world’ clinically-managed patients. Therefore, the angiographic substudy of the TRIAS Program is planned after the primary endpoint at 1 year, thereby not influencing the rate of nonclinically-driven revascularization.

To date, limited data is available regarding the safety and efficacy of the ECS. In the HEALING-FIM the safety of the ECS was evaluated in 16 clinically stable patients with simple, de novo coronary artery lesions. At 6 months, angiographic follow-up with intravascular ultrasound imaging (IVUS) was performed, showing a mean late loss of 0.63 ± 0.52 mm and a percent in-stent restenosis of 27.2 ± 20.9%. At 9 months clinical follow-up, the composite of cardiac death, stroke, MI, and TVR was 6.3% with no cases of stent thrombosis. The nonrandomized HEALING II study enrolled 63 patients with de novo coronary artery lesions. The composite of cardiac death, MI, and TLR was 7.9% at 18 months and predominantly due to the clinically driven TLR rate of 6.3%. No ST was observed during the 18 months of follow-up. At 6 and 18 months, serial angiography with IVUS imaging was performed and a significant late regression of neointimal hyperplasia was observed between 6 and 18 months, showing a reduction in LL of 24.4% (LL: 0.78 ± 0.39 mm vs 0.59 ± 0.31 mm, respectively) and a reduction in IVUS percent volume obstruction of 11.4%.

In a single-center, nonrandomized study by Miglionico et al, 80 patients with a high risk of restenosis were evaluated at 14 months, showing a TLR of 13% and a composite of cardiac death, MI, or TVR of 16%. Interestingly, no cases of definite stent thromboses were observed. In the multicenter, international e-HEALING registry the ECS was evaluated in an all-comers patient population and enrollment of the 5000 patients was completed in October 2007. Preliminary data on the 1-year clinical outcome of the first 3196 patients were presented during scientific sessions at the TCT’08 (De Winter) and AHA’08 (Silber) and showed a composite of cardiac death, MI and TLR of 8.5% and a clinically driven TLR of 5.0%. These results are comparable to reports of the ARRIVE registry evaluating the PES and e-CYPHER registry evaluating the sirolimus-eluting stent.

In the Academic Medical Center, single-center TRIAS HR study, 193 patients with high-risk lesions were randomized to either an ECS or a PES. Although randomized, there was a significant difference in diabetic patients (14% ECS vs 27% PES; p = 0.025) and in small vessels treated (7% ECS vs 20% PES; p = 0.004). At 1-year follow-up, the composite of cardiac death, MI and TVR was 17.3% in the ECS group versus 10.5% in the PES group (p = 0.17). Recently, the 2-year follow-up was presented at the EuroPCR 2009 convention.
Between 1 and 2 years follow-up, 2 patients in the ECS group and 6 patients in the PES group underwent a TLR resulting in a composite of cardiac death, MI and TVR 20.4% vs 15.8% respectively (p = 0.29) at 2-years; a catch up trend of the DES group as compared to the 1-year results. Noteworthy, no patients suffered a stent thrombosis up to 2 years in the ECS group, while 4.2% of patients in the PES group did (p = 0.059).

In conclusion, the ongoing TRIAS Program is a multicenter, international, randomized study to determine the clinical efficacy of the ECS in 2560 clinically stable patients with de novo coronary artery disease in either lesions carrying a low risk or high risk of restenosis. The first results are expected in 2010.
References


