

A European multicentre, randomised study of the MAR-Tyⁿ cobalt chromium tin-coated stent in patients with *de novo* coronary artery lesions: study design and protocol

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The authors have no conflict of interest to declare.

KEYWORDS

Coronary artery disease, restenosis, stent, cobalt chromium stent, study design

Abstract

Aims: The aim of this randomised study is to evaluate the efficacy and safety of a new bare metal stents (BMS) with thin struts and a novel passive coating as compared to current standard BMS.

Methods and results: We designed an international, multicentre, randomised trial planned to include 160 patients assigned to receive either the titanium-nitride coated MAR-tyⁿ stent (International Biomedical Systems, Trieste, Italy) or the Vision stent (Abbott Vascular, Abbott Laboratories, Abbott Park, IL, USA). Patients with left main or bypass graft disease, complex coronary lesions, needing treatment of multiple lesions, with recent myocardial infarction, prior BMS in or within 5 mm of the target lesion, left ventricular ejection fraction $\leq 25\%$ and at increased bleeding risk are excluded. All patients are treated with dual anti-platelet therapy for two months. The primary endpoint is in-stent late luminal loss (LL) at 6-month follow-up angiography. Secondary endpoints are the incidence of major adverse cardiovascular events (MACE) and stent thrombosis over 12 months after randomisation. Patients' enrolment is open in all centres.

Conclusions: This study will address the important question of safety and efficacy of a novel, inert and highly compatible passive coating on a thin-strut BMS with a great potential to be superior to a non-coated widely used BMS.

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Introduction

The ISAR-STEREO trials^{1,2} have demonstrated that geometric properties of metallic stents are strong determinants of restenosis rate, in that thinner struts of bare metal stents (BMS) have a favourable effect on restenosis in respect to more bulky prostheses. In the latter years new generation BMS have been developed, that are constructed with alloys such as cobalt-chromium (Co-Cr) and have extremely thin struts, although retaining excellent mechanical properties and biocompatibility. The Numen stent (International Biomedical Systems, Trieste, Italy), is a 65 micron thick Co-Cr BMS with reduced stent mass and optimal radial strength recently marketed, with good clinical results³.

In the meantime, several drug-eluting stents (DES) have demonstrated to be superior to BMS in terms of restenosis prevention. However BASKET-LATE⁴ study showed an excess of late clinical events related to late stent coronary thrombosis in patients treated with drug-eluting stents (DES) compared to those with bare-metal stents (BMS). Afterwards, this observation was confirmed in a pooled analysis of the pivotal DES trials,⁵ in a meta-analysis of available prospective randomised trials,⁶ and in large registries^{7,8}.

Since re-endothelialisation of the strut surface is a key factor for arterial healing and thrombosis prevention, and passive coating with an extremely thin layer of a highly biocompatible material, such as ceramics (titanium nitride) may improve this process, pre-clinical studies have been undertaken in order to demonstrate healing properties of the Numen coated stent MAR-tyⁿ (International Biomedical Systems, Trieste, Italy). The bare metal Numen stent is a slotted tube low profile coronary stent manufactured by laser cutting of a L605 cobalt-chromium alloy. Its main characteristics are reduced strut thickness and total stent volume without compromise of radial strength and radiopacity. Beside this, the design of the Numen stent is based on the Less Mismatch Theory to reduce the impact on artery wall and motion³. The design consists of elementary sinusoidal peaks, where the number of peaks around the circumference varies according to the diameter and the levels are connected using thin, 45° oriented connectors. The stent is coated with an inert titanium nitride (TiN) layer, that creates a barrier to toxic metal ions diffusion and a very smooth surface. TiN coating is used commercially for its hard-wearing and chemical inactive properties, particularly for surgical tools. TiN has chemical stability, great hardness, excellent wear properties, low electrical impedance, biocompatibility, haemocompatibility and can be manufactured as a nanocrystalline structure to produce a chemical surface more suitable for endothelial cells. The produced coating is very fine and with a porosity within the film structure of less than 10 nm in diameter. A first animal study (rabbit iliac artery model) confirmed both the high degree of adhesion between the coating and the metal alloy in expansion tests without any loss of coating, and the *in vivo*, the safety of the TiN coated stent⁹. A recently reported¹⁰ animal study showed that the degree of re-endothelialisation with the MAR-Tyⁿ stent was improved as compared to Vision stent. Previously Windecker and co-workers demonstrated that a Titanium-Nitride-Oxide (TiNOX) coated stent was superior to an identical stainless steel stent in terms of restenosis¹¹.

The main aim of MAR-Tyⁿ study is to assess whether these pre-clinical positive results are translated into an advantage in clinical settings. Patients will be randomly assigned to either the TiN coated MAR-Tyⁿ (International Biomedical Systems, Trieste, Italy) or the cobalt-chromium BMS (Vision, Abbott Vascular, Abbott Laboratories, IL, USA) chosen as a widely used representative of the third generation BMS. The primary endpoint will be the 6-month angiographic in-stent late loss. A specific substudy using optical coherence tomography (OCT) will evaluate cellular lining coverage of stent struts and stent apposition at follow-up.

This paper describes the study rationale, design, set-up and statistical methodology.

Methods

Patients

A series of 160 patients (80 patients/study arm) will be enrolled. They have to be older than 18 years of age, with documented ischaemia (symptomatic or silent with positive stress test) and with *de novo* native coronary artery lesions between 10 and 22 mm in length and 2.5 mm to 3.5 mm in diameter (by visual estimation). Exclusion criteria included recent myocardial infarction (<1 week), in-stent restenosis, thrombosis, heavily calcified lesions, bifurcation lesions, target lesion in unprotected left main coronary artery or a bypass-graft, need for treatment of multiple lesions, need for oral anticoagulation therapy, increased risk of bleeding, known intolerance of aspirin and/or clopidogrel, expected low patient's compliance, and impossibility to perform required follow-up. A log book will be used in all centres for recording all patients being treated by PCI and stenting during the entire study period. This will enable assessment of the percentage of patients not enrolled and the reasons for being excluded.

Randomisation, data collection and monitoring

Patients will be randomised 1:1 to MAR-Tyⁿ or Vision through a website, using an on-line randomisation system. All patient data will be collected on a dedicated electronic case report form and transmitted via the Internet to a central database at the data centre. All centres will be regularly monitored for source data documentation and missing or questionable data will be completed and corrected by queries. All events will be reviewed and adjudicated periodically by a Clinical Events Committee (CEC).

Percutaneous coronary intervention procedures

Percutaneous coronary intervention will be performed according to the standard techniques at the discretion of the operators in each centre; however, direct stenting will not be allowed. Size of the vessel will be assessed visually after intracoronary injection of nitroglycerine. Although the study is intended as a single stent implantation study, in the case two or more stents are required in the same lesion, all stents will have to be of the same type. Stents should be expanded as much as possible and as feasible. Lesion/s will be filmed in at least two orthogonal views pre- and post-intervention. Angiograms will be collected and sent to the centralised core angiographic laboratory for quantitative coronary angiography (QCA) evaluation.

Quantitative coronary angiography

The offline quantitative coronary angiography analyses will be done at the Rome Heart Research Laboratory by technicians who are blinded to the treatment. All the angiographic measurements will be done in two orthogonal views and applying a validated methodology. An automated edge detection algorithm (Q angio XA, 7,1; MEDIS, Leiden, The Netherlands) will be adopted.

Concomitant therapy

All patients will be given aspirin 100 mg daily for the long term after an appropriate loading dose if not already on aspirin. Clopidogrel will be prescribed at a dose of 75 mg/d for two months in all patients irrespective of stent type used, after a loading dose of at least 300 mg. All other medication will be given at the discretion of the physician in charge as clinically indicated.

Follow-up

A clinical follow-up by outpatient visit will be performed after one, six and 12 months. The visit report will include information regarding symptoms, vital signs, intercurrent major adverse cardiac events (definition see below), major bleeding events (definition see below), drug and other treatments, and hospitalisations. This will be verified by primary care physician and/or hospital charts and death certificates. Follow-up angiography will be performed at six months, or earlier if clinically indicated, and all angiograms will be sent to the core QCA laboratory.

Endpoints

The primary endpoint is angiographic in-stent late loss (LL) calculated as the arithmetic difference between final post-procedure minimal luminal diameter (MLD) and MLD at follow-up angiography. Secondary endpoints are:

- Composite of major adverse cardiac events (MACE) defined as death, myocardial infarction (Q wave and non-Q wave), emergent bypass surgery, or repeat target lesion revascularisation over 12 months.
- Angiographic binary restenosis ($\geq 50\%$ diameter stenosis) six months post-procedure.
- In-lesion MLD at six months post-procedure.
- Target lesion revascularisation (TLR) at 12 months post-procedure.
- Target vessel revascularisation (TVR) at 12 months post-procedure.
- Target vessel failure (TVF) defined as cardiac death, myocardial infarction, or target vessel revascularisation at 12 months post-procedure.
- Device success defined as achievement of a final residual diameter stenosis of $< 50\%$ (by QCA), using the assigned device only.
- Lesion success defined as the attainment of $< 30\%$ residual stenosis (by QCA) using any percutaneous method.
- Procedure success defined as achievement of a final diameter stenosis of $< 30\%$ (by QCA) using any percutaneous method, without the occurrence of death, myocardial infarction (MI), or repeat revascularisation of the target lesion during the hospital stay.

Definitions

Cardiac death is defined as any death not explained by other known reasons such as cancer, suicide, accident, etc. MI is defined according to the standard definitions by the European Society of Cardiology¹⁷ with peri-interventional MI diagnosed in the presence of a 3-fold increase of CK MB above the upper limit of normal in each laboratory. TVR is any revascularisation of the index vessel treated by PCI and stenting at study entry. To avoid double counting of MI-related events, TVR will be divided into MI-related and non-MI-related TVRs. Late and very late stent thromboses are defined according to the Academic Research Consortium (ARC) definitions using “definite” and “probable” as indicative of clinically relevant stent thrombosis¹⁸. Bleedings are defined according to the Thrombolysis in Myocardial Infarction (TIMI) definitions: major, intracranial haemorrhage or clinical signs of haemorrhage with a drop in haemoglobin > 5 g/dL; minor, any clinical sign of haemorrhage with a fall in haemoglobin of 3 to 5 g/dL; significant, major and minor bleedings together. A net clinical benefit of one versus the other stent type is defined by a reduction in the combined rate of TVR without death, MI, or significant bleeding. All clinical endpoints will be adjudicated by an independent critical events committee blinded to the stent used.

Statistics

The analysis of efficacy and safety will be performed based on the intention-to-treat principle. Primary end-point will be analysed on a per-protocol basis. Baseline characteristics of the study population by randomised groups will be analysed by descriptive statistics. Continuous variables will be presented as mean \pm SD while categorical variables will be expressed as counts and percentages. Mean difference in LL (primary endpoint) between randomised groups will be evaluated by analysis of variance (ANOVA) adjusting for covariates such as sex, age, indication to PCI, diabetes, hypercholesterolaemia, use of GPIIb/IIIa inhibitors etc., which may result unbalanced between treatment groups, taking into account differences across sites if present. The 95% confidence intervals for the mean difference will be provided.

Quantitative angiographic endpoints will be analysed only in patients with two evaluable angiograms as mean differences between randomised groups by means of the analysis of variance and 95% confidence intervals for the mean difference will be provided. Only matching projections will be used.

Each of the secondary endpoints expressed in terms of rates will be analysed by means of a logistic regression model and estimates of the relative risk along with 95% confidence interval will be provided. The cumulative incidence of adverse events will be estimated according to the Kaplan-Meier method and the log-rank test will be employed to evaluate differences between groups.

Statistical significance will be declared if the two-sided P-value is < 0.05 . All statistical analyses will be performed using the SAS® System, version 9.2 (SAS Institute Inc, Cary, NC, USA).

Based on reported values for BMS, and the preclinical results of the MAR-Tyⁿ stent¹⁰, we assumed an in-stent LL of 0.90 ± 0.67 mm in the control stent group and a 0.60 ± 0.60 mm in the MAR-Tyⁿ stent

group. Therefore to detect a mean difference in LL of 0.30 mm (pooled SD=0.65 mm) with an α error level of 5%, power 80% and assuming a patient drop-out rate of 10%, enrolment of 160 patients is required.

Timetable

The seven centres involved in this study perform about 6,000 PCIs per year in total. Assuming that 3-5% of these patients can be included in this study, recruitment is expected to be completed within about one year.

The study protocol was approved by the Ethics Committee of the Area Vasta Romagna, Cesena, Italy, in July, 2008. The first patient was included in Ravenna on September 16, 2008, with the other centres following gradually. Thus, we aim to include the last patient in the autumn of 2009 and complete 1-year follow-up in the autumn of 2010.

Study organisation

MAR-Tyⁿ is a prospective randomised multicentre trial involving seven centres, four in Italy and one each in Switzerland, Germany, and The Netherlands. The leading centre is in Ravenna, Italy, while the location of the Data Management Centre of the study is in the Mario Negri Centre, Milan, Italy. The principal investigator, the steering committee, all investigators, the independent critical events committee, QCA CoreLab, Data and Monitoring Centres are listed in Appendix A.

The study is supported by International Biomedical Systems, Trieste, Italy. Of note, the company had no role whatsoever in the design or protocol of this study nor will it be involved in the analysis or interpretation of the results.

Ethics

The study protocol was approved first by the Ethics Committee of the Area Vasta Romagna of Cesena, Italy, and was consecutively submitted to the ethics committees of all participating centres for approval. All patients have to sign a written informed consent form for participation in this trial. The trial is performed according to the Helsinki agreements¹⁹. The trial has been registered in the International Standard Randomised Controlled Trial Number Register (NCT00637104).

Discussion

DES reduce restenosis and related clinical events during the first year after stent implantation,^{6,12-16} however the longerterm overall clinical benefit seems less clear owing to the rare but clinically relevant problem of late events related to very late stent thrombosis. One of the major determinants of ST is thought to be incomplete re-endothelialisation caused by the specific drug and/or the non-resorbable polymer coating of the stent surface. At the same time newer stent designs, alloys and specifically designed coatings are developed with the intention to combine effective restenosis prevention with a complete recovery of normal endothelial tissue at the site of stent implantation¹¹. The latter is aiming at a protective effect against stent thrombosis. MAR-Tyⁿ stent shows high biocompatibility and strong adhesion of TiN to the metal alloy⁹, and

is particularly effective in producing a complete and rapid stent coverage in pre-clinical studies¹⁰. The MAR-Tyⁿ stent has the potential to demonstrate the possibility of achieving reduced neointimal response together with a complete re-endothelialisation of stent in man. Evaluation of two endpoints, specifically the 6-month in-stent LL and 12-month clinical events, and comparison with the results in the control group of the cobalt-chromium Vision stent as well as the use of OCT in a subgroup of patients will help to verify the expected advantages of this novel stent in man. If confirmed, the MAR-Tyⁿ stent might provide a safe alternative to currently available DES.

Appendix A

Steering Committee: A. Kastrati, (Chairman), E. Camenzind, A. Branzi, E. Mangieri

Principal investigator: M Balducelli, Ravenna, Italy

Site Monitoring: Pharma Part AG, Thalwil -Switzerland

Data Management: Istituto di Ricerche Farmacologiche "Mario Negri" Dipartimento di Ricerca Cardiovascolare (Cardiovascular Research Department) Milano, Italy

QCA Core Lab: Rome Heart Research S.r.l., F. Prati Rome Italy

Data and Safety Monitoring Board: G. Biondi Zoccai, M.Viecca, J. Moreu

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