MINVASYS

CLINICAL DATA

Amazonia®

Sir

Sirolimus Elution

May 2018

INDEX

1 INTRODUCTION

Anti-proliferative drug used on stents reduce smooth muscle cell proliferation and neointimal hyperplasia, the principal cause of restenosis after coronary stenting. Drug-Eluting Stents (DES) usually use limus family (Sirolimus, Zotarolimus, Everolimus) and Paclitaxel. Both type of drugs are highly lipophilic and show rapid and strong uptake in arterial wall tissue. Compared to Bare-Metal Stents (BMS), the first-generation of DES have drastically reduced rates of restenosis and need of target lesion revascularization [1, 2].

However, concerns have been raised regarding their long-term safety [3, 4]. The presence of a permanent polymer coating may cause stent thrombosis as a result of delayed healing and a hypersensitivity reaction in some cases.

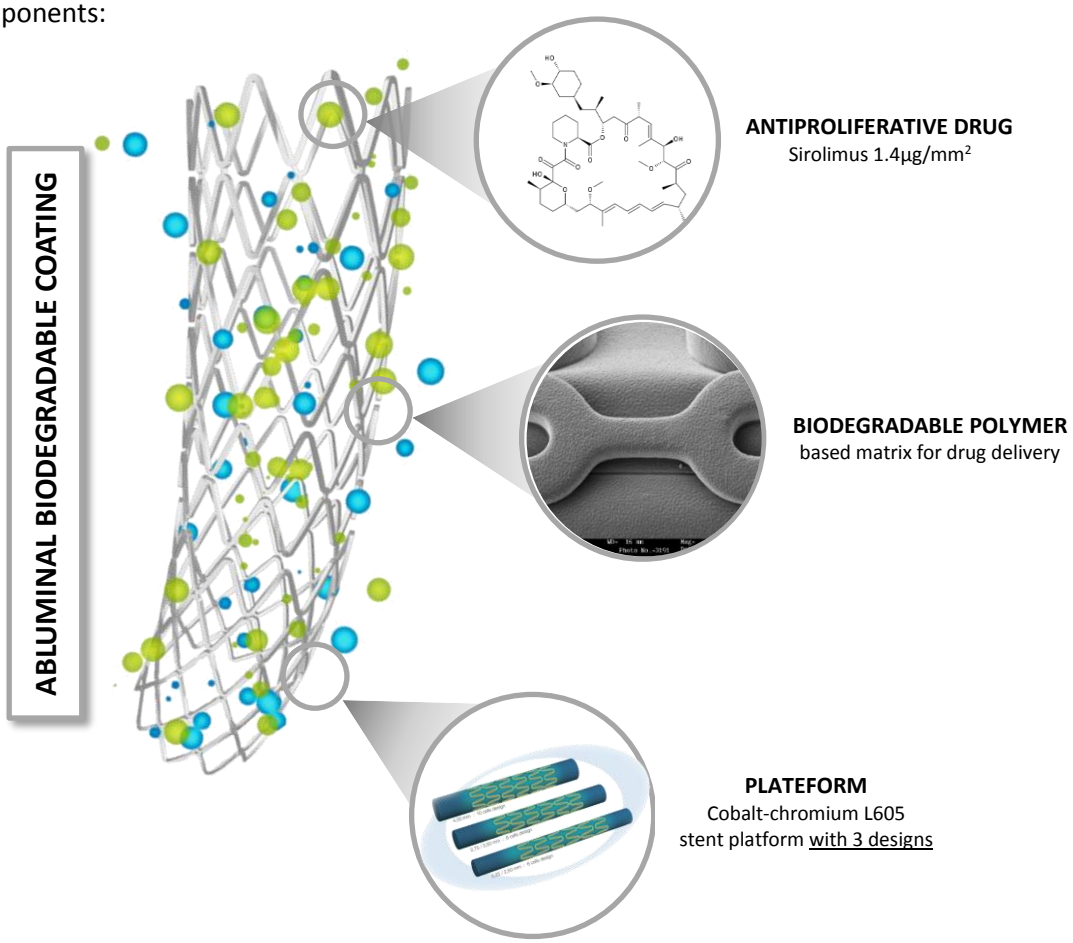
To address this issue, new generations of DES incorporate thin strut stent platform, biodegradable, biocompatible polymers as vehicles for drug delivery.

MINVASYS developed the Amazonia SIR, a thin strut Sirolimus-Eluting Stent (SES) with Biodegradable-Polymer (BP) matrix for the treatment of coronary artery diseases.

The safety and efficacy of the Amazonia SIR stent were evaluated through a first-in-man study and an e-Registry. Results obtained will be presented in this booklet.

2 DEVICE DESCRIPTION

The Amazonia SIR is a biodegradable polymer based drug eluting coronary stent. The device includes three main components:



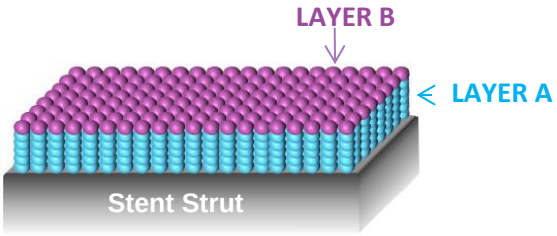
Anti-proliferative drug - Sirolimus

The device coating is a combination of inactive and active component. The active component is an anti-proliferative drug, sirolimus. Sirolimus also known as rapamycin, is an immunosuppressant drug that prevents activation of T cells and B-cells by inhibiting their response to interleukin-2 (IL-2).

The anti-proliferative effect of sirolimus prevent restenosis in coronary arteries. Sirolimus is formulated in blend of polymer coating that provides controlled release for a longer duration post coronary intervention.

Biodegradable polymers

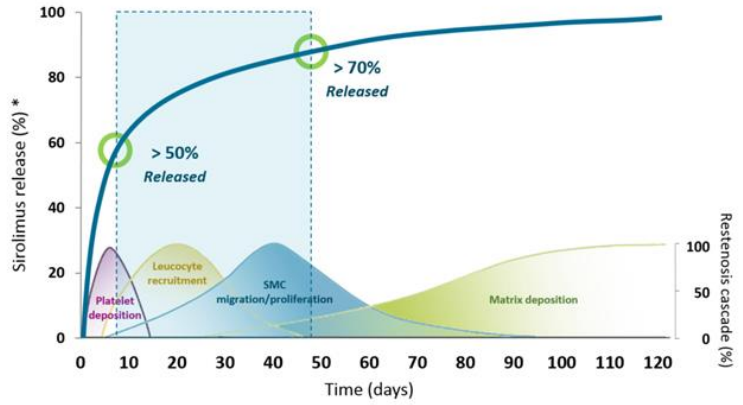
The inactive component is a Poly L-lactide based family of polymer (biodegradable and biocompatible polymer) which is released with the drug and totally degraded after 6 to 8 months.

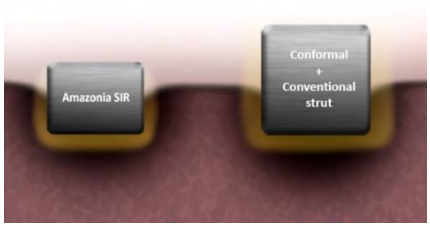


LAYER A - **Sirolimus drug** and **Poly-L lactic Acid** (PLLA), **Poly(lactic-co-glycolic) acid** (PLGA), **Polyvinylpyrrolidone** (PVP)
Bio-absorbable, biocompatible and non-toxic polymers.
LAYER B - **Poly Vinyl Pyrrolidone** (PVP)
100% Protective layer without drug.
Biodegradable, water soluble polymer.

Sirolimus controlled elution

The combination of two layers coating technology and abluminal drug distribution ensure an effective and controlled elution of sirolimus to arterial wall, and therefore perfectly adapted to prevent natural adverse effects of healing process.



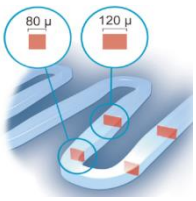


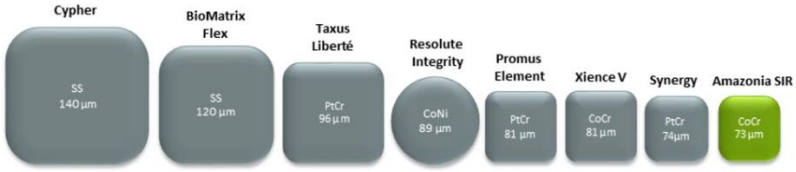
Stent platform

The stent platform is made of cobalt-chromium alloy (L605) that has been successfully used in other implantable medical devices since 1985. The delivery system is a Rapid exchange (RX) system.

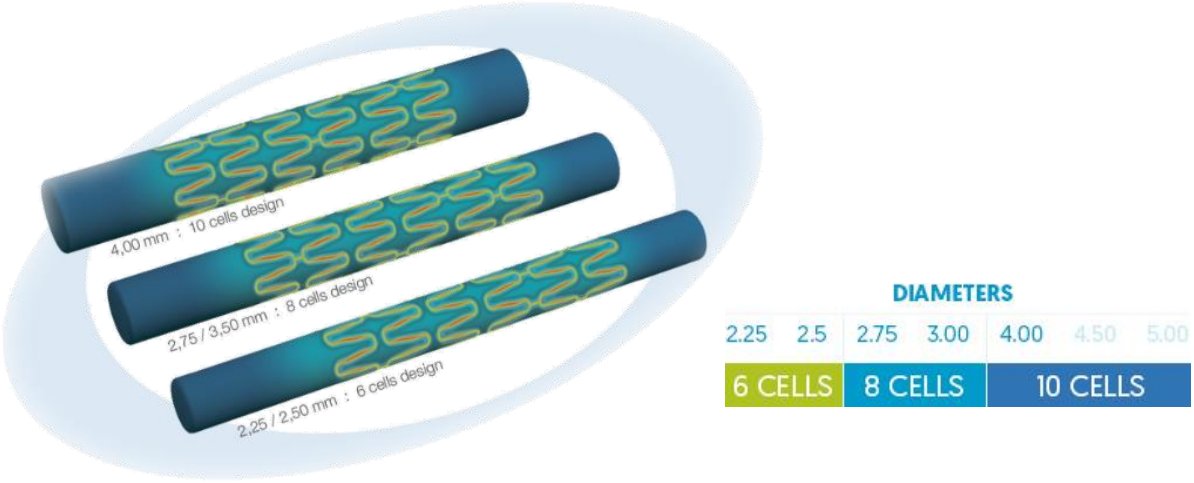
Amazonia SIR has a unique thin strut design that allows more flexibility, homogenous stent deployment and larger contact surfaces:

- Constant thickness: 73 µm
- Narrow radius width: 80µm
- Larger strut width: 120 µm





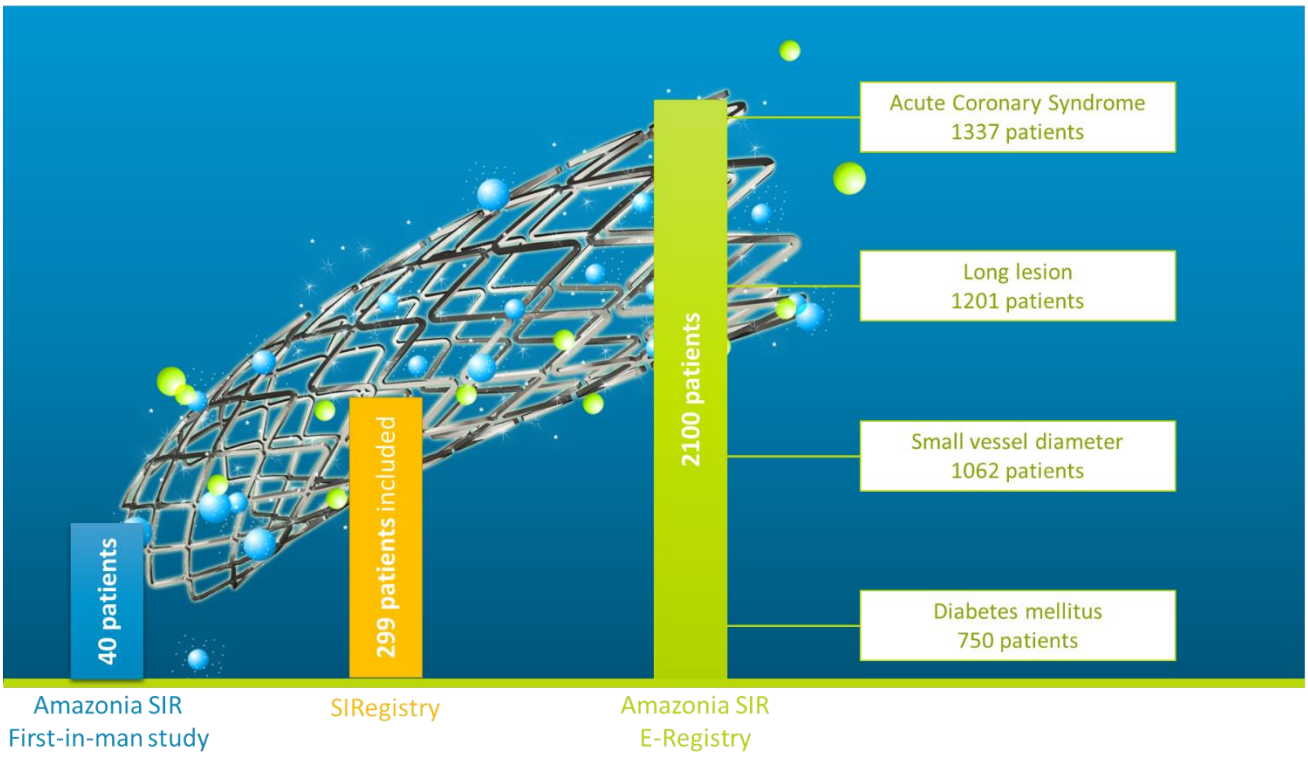
Amazonia SIR has an open cell design and has three stent platform designs adapted to vessel diameter with metal/artery ratio of 14%.



3 CLINICAL PROGRAM

The safety and efficacy of the Amazonia SIR were assessed through clinical studies:

- An interventional, first-in-man study with 40 all comers real world patients included,
- A prospective, observational and multicenter study with to date 299 patients included,
- A prospective, multicenter registry with to date 2100 patients included.



4 First-in-man clinical investigation of the Amazonia SIR stent

AIMS

The purpose of the present study is to capture the clinical and angiographic results of patients receiving the Amazonia SIR stent with sirolimus drug and biodegradable polymer matrix on cobalt-chromium platform.

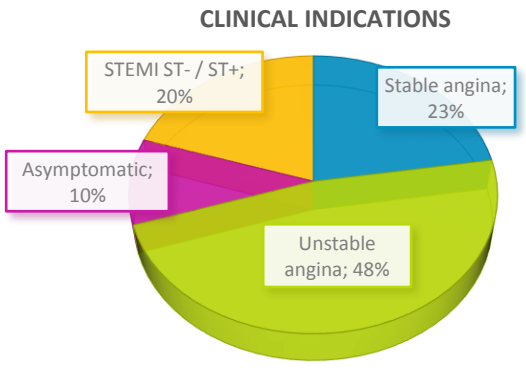
METHODS

Between February 2012 and September 2012, 40 patients with coronary artery diseases were treated with the Amazonia SIR drug eluting stent in India. The primary endpoint was the evaluation of the in-stent Late Lumen Loss (LLL) at 6 months by Quantitative Coronary Analysis (QCA). Angiographic results were analyzed by an independent core laboratory. Secondary endpoints included notably: device and lesion success and Major Adverse Cardiac Events (MACE: cardiac death, Myocardial Infarction (MI) and Target Lesion Revascularization (TLR)). Clinical follow-up was scheduled at 1, 6, 12 and 24 months.

Patients' and lesions' baseline characteristics are presented hereafter:

POPULATION	
Patient, n	40
Age, years	53.8±10.0
Male, %	77.5
RISK FACTORS	
Hypertension, %	62.5
Hypercholesterolemia, %	7.5
Diabetes, %	10.0
History of CAD, %	
-History of MI, %	27.5
-History of stroke, %	2.5
-Previous CABG, %	10.0

LESIONS CHARACTERISTICS	
Nb lesions treated, n	56
Length, mm (mean±SD)	19.8±14.2
Lesion class (ACC/AHA), % - A - B1 - B2 - C	 14.3 19.6 30.4 35.7
Target vessel, % - LAD - LCx - RCA	 58.8 17.6 23.6



RESULTS

Procedural data

The Amazonia SIR stent implantation was performed according to the Instruction for Use (IFU). There were 56 lesions treated with a mean lesion length of 19.8±14.2mm. The reference vessel diameter was 2.46±0.45mm. The mean stent length and diameter were 27.4±8.8mm and 3.4±4.1mm respectively.

Predilatation was performed in 80.4% of patients. The device was inflated at a mean pressure of 13.8atm for a mean time of 28.0sec. 16.1% of patients received an additional stent and post-dilatation was performed in 30.4%. There were no procedure complications and no adverse cardiac events at discharge.

Angiographic follow-up at 6/9 months

Angiographic control between 6 and 9 months post-procedure was performed in 39 patients (97.5%). For angiographic outcomes see Table 1.

Table 1: Angiographic results in 39 patients

Mean±SD	In-stent	In-segment
Pre-procedure		
Reference Vessel Diameter (RVD), mm		2.46±0.45
Minimum Lumen Diameter (MLD), mm		0.71±0.39
Percent Diameter Stenosis (DS), %		71.8±14.6
Post-procedure		
RVD, mm		2.61±0.43
MLD, mm	2.40±0.40	2.22±0.41
%DS, %	6.9±6.7	15.1±7.5
Acute gain, mm	1.70±0.42	1.51±0.44
6 months follow-up		
RVD, mm		2.53±0.43
MLD, mm	2.17±0.54	2.06±0.51
%DS, %	14.1±14.4	19.0±13.3
Late Lumen Loss, mm	0.24±0.30	0.17±0.29

Clinical follow-up results

All included patients were followed after hospital discharge up to 2 years after the index procedure. The follow-ups were obtained through telephone contacts in order to have information regarding patients' medical history, cardiovascular drug use and adverse events at 1, 3, 6, 12 and 24 months. Up to 24 months there were no stent thrombosis reported and the MACE rate was 3.7%.

PATIENT CASE

Age: 47 years

Gender: Male

Clinical condition: Thrombolytic myocardial infarction – Single vessel coronary artery disease.

Coronarography: 70-80% diffused stenosis in mid-distal RCA (Figure 1).

Strategy: Percutaneous coronary intervention with placement of a 3.50x36mm Amazonia SIR Sirolimus-eluting stent in RCA.

Acute results: The angiography results post-procedure was very satisfactory (Figure 2).

Follow-up results: At 9 months angiographic follow-up, the angiography showed an excellent patency of the obtuse marginal without any MACE or stent thrombosis was observed (Figure 3).

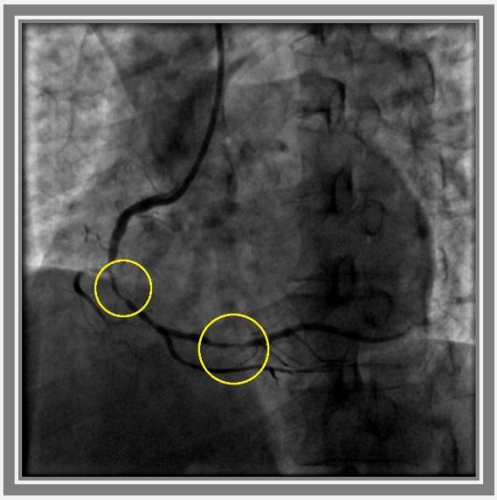


Figure 1: Pre-procedure

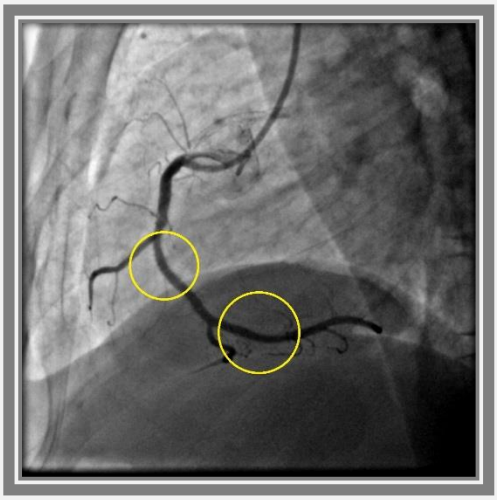


Figure 2: Post-procedure

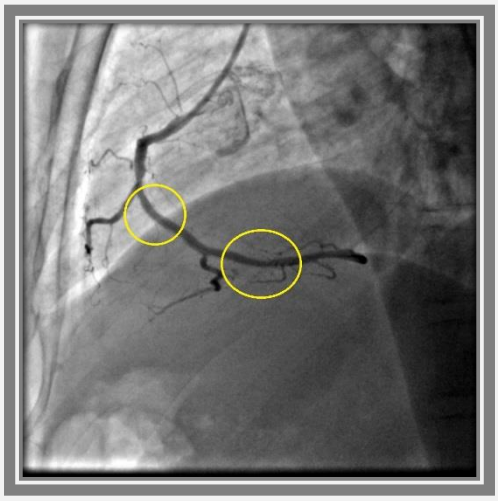


Figure 3: Follow-up

CONCLUSIONS

Long-term safety results of the first-generation DES led to some concerns particularly regarding stent thrombosis. The exact reason that might have caused this complication is still unclear but safety of both the drug and the permanent polymer coating have been questioned. These concerns have led to the development of polymer-free and biodegradable polymer stents.

In this Amazonia SIR First-in-man, real-world study, there was a very low rate of reported adverse event throughout the study. Moreover, the angiographic follow-up results between 6 and 9 months were excellent, with a measure of in-segment late lumen loss of 0.17±0.29mm and an in-stent percent diameter stenosis of 19.0% at follow-up. These results demonstrated the safety and efficacy of the Amazonia SIR stent, however this Amazonia SIR study was a first-in-man single center clinical evaluation and therefore was limited by a small patient cohort. These results have been confirmed in a larger cohort registry with long-term safety and effectiveness of the Amazonia SIR biodegradable polymer stent.

5 Amazonia SIR e-Registry

AIMS

The purpose of the Amazonia SIR e-Registry is to assess long-term safety and efficacy of the Amazonia SIR sirolimus-eluting stent with biodegradable-polymer matrix.

METHODS

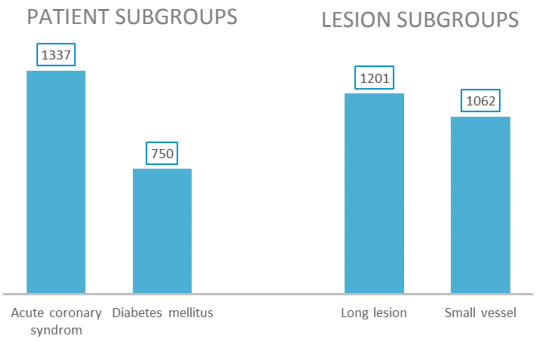
The Amazonia SIR e-Registry is an all-comers study that reflects routine clinical practice of the treatment of coronary artery disease. The objective is to enrol 3,000 patients in this prospective and multicentre e-Registry. To this date, 2100 patients with coronary artery diseases were treated with the Amazonia SIR sirolimus-eluting stent. Among these patients we distinguished 4 types of clinical presentation (patients can belong to more than one group): Acute Coronary Syndrome (ACS), long lesion, Small Vessel Diameter (SVD) and diabetes mellitus.

Patients will be followed up clinically at 1, 3, 9, 12 and 24 months post-procedure. Angiographic follow-up at 9 months will be performed only on patients who give their consent. The study endpoints were procedural success and MACE rate at 12 months.

Patients' and lesions' baseline characteristics are presented hereafter:

POPULATION	
Patient, n	2100
Age, years	57.73±10.93
Male, %	78.8
RISK FACTORS	
Hypertension, %	43.9
Diabetes, %	35.7
History of CAD,	
-Previous MI, %	13.0
-Previous PCI, %	5.3
- Prior CABG, %	1.9

LESIONS CHARACTERISTICS	
Nb lesions treated, n	2487
Target vessel, % - LMCA - LAD - LCx - RCA - Graft	 0.6 49.3 20.9 27.3 0.4



RESULTS

The overall results obtained through all patients included will be presented first, then subgroups analysis of small vessel diameter, long lesion, acute coronary syndrome and diabetes mellitus patients will be introduced.

Procedure data

The mean stent length and diameter used were 26.50±8.77 mm and 2.93±0.43 mm respectively. A rate of <80% patients had a lesion pre-dilatation and >30% had a lesion post-dilatation.

Clinical follow-up results in all patients

The follow-ups were obtained through telephone contacts in order to have information regarding patients' medical history, cardiovascular drug use and adverse events at 1, 3, 9, 12 and 24 months. To this date, the follow-ups are on-going and all patients did not reached all the time points.

Results included in the following table present outcomes for all patients that achieved their follow-ups.

Table 2: Clinical follow-ups results up to two years

Follow-up	1 month	12 months	24 months
Number of patients	2100	1744	1260
MACE*	0.57% (12)	2.24% (39)	3.17% (40)
Cardiac death	0.19% (4)	0.23% (4)	0.32% (4)
TV-MI	0.33% (7)	0.46% (8)	0.63% (8)
TLR/TVR	0.05% (1)	1.55% (27)	2.22% (28)
ST (ARC def/prob)	0.48% (10)	0.63% (11)	0.87% (11)

**MACE: cumulative MACE defined as number of death, TLR and MI.*

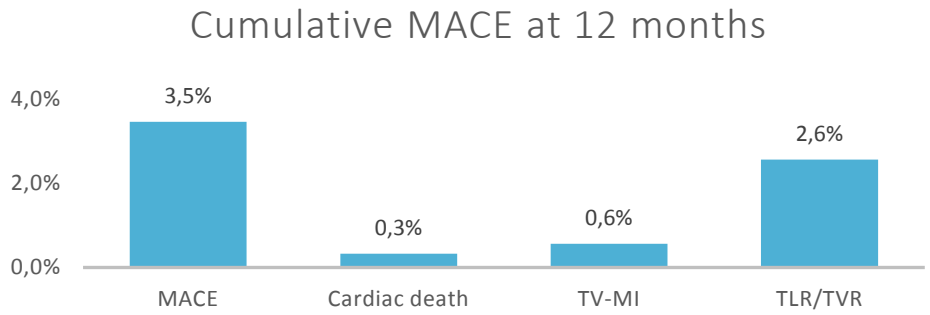
SMALL VESSELS SUBGROUP ANALYSIS

Clinical follow-up results in patients with small coronary lesions

A total of 1062 patients with 1151 small coronary vessel lesions (Ø≤2.75mm) were treated with the Amazonia SIR stent.

These patients were clinically followed at 1, 3, 9, 12 and 24 months post-procedure. To this date, the follow-ups are on-going and all patients did not reach all the required time points.

To the date of the analysis, 899 patients reached the 12 months' clinical follow-up. The preliminary MACE results are detailed in the following Figure.



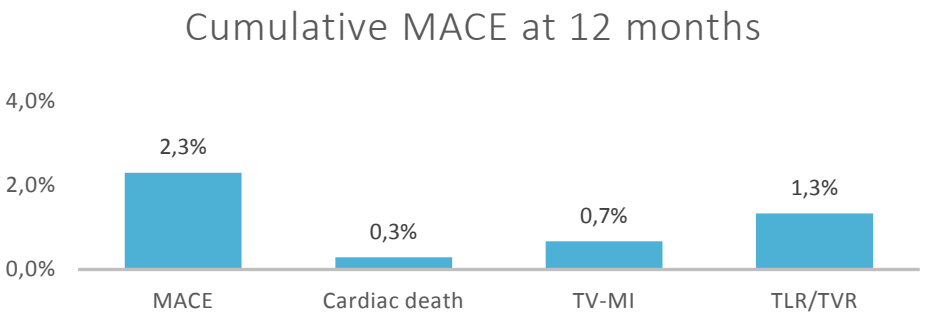
ACUTE CORONARY SYNDROME SUBGROUP ANALYSIS

Clinical follow-up results in patients with acute coronary syndrome

A total of 1337 patients presenting acute coronary syndrome were treated with the Amazonia SIR stent.

These patients were clinically followed at 1, 3, 9, 12 and 24 months post-procedure. To this date, the follow-ups are on-going and all patients did not reach all the required time points.

To the date of the analysis, 1050 patients reached the 12 months' clinical follow-up. The preliminary MACE results are detailed in the following Figure.



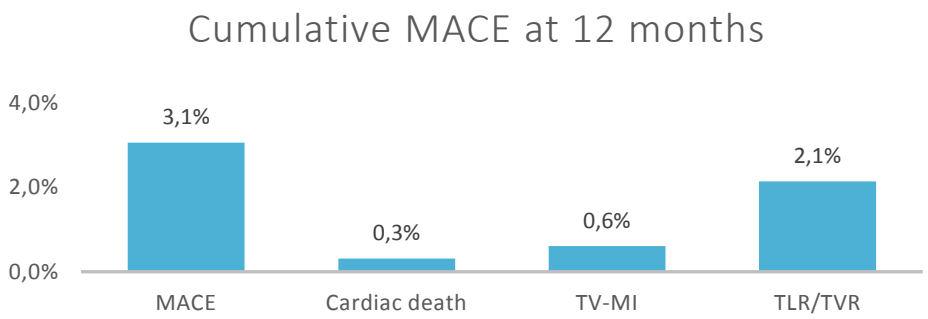
LONG LESION SUBGROUP ANALYSIS

Clinical follow-up results in patients with long coronary lesions

A total of 1201 patients with long lesions (≥28mm) were treated with the Amazonia SIR stent.

These patients were clinically followed at 1, 3, 9, 12 and 24 months post-procedure. To this date, the follow-ups are on-going and all patients did not reach all the required time points.

To the date of the analysis, 981 patients reached the 12 months' clinical follow-up. The preliminary MACE results are detailed in the following Figure.



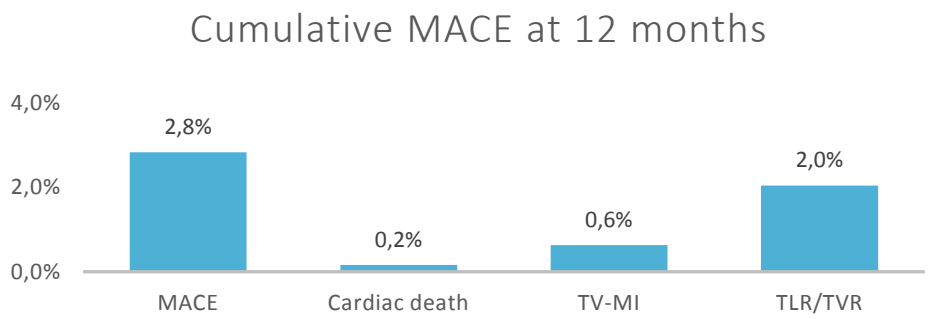
DIABETIC PATIENTS SUBGROUP ANALYSIS

Clinical follow-up results in diabetic patients

A total of 750 diabetic patients with a total of 907 lesions were treated with the Amazonia SIR stent.

These patients were clinically followed at 1, 3, 9, 12 and 24 months post-procedure. To this date, the follow-ups are on-going and all patients did not reach all the required time points.

To the date of the analysis, 637 patients reached the 12 months' clinical follow-up. The preliminary MACE results are detailed in the following Figure.



CONCLUSIONS

Interim analysis has revealed very low rates of major adverse cardiac events for patients that reached the follow-up time points. Indeed, the overall MACE results were below 4% even at long-term follow-up at 24 months with only 3.17% of cumulative MACE.

The MACE rate results observed in the subgroups were also very low confirming that the Amazonia SIR stent is safe and efficient in routine clinical practice with for example patients presenting whether acute coronary syndrome, diabetes mellitus, small vessel or long coronary lesions.

6 SIRegistry

AIMS

The purpose of this study is to assess the safety, performance and effectiveness of the Amazonia SIR Sirolimus-Eluting Coronary Stent for the treatment of lesions in native coronary arteries in the real-world clinical practice.

STUDY DESIGN

The SIRegistry is a prospective, worldwide multicenter, internet-based, observational study. The primary endpoint is the rate of Major Adverse Cardiac Events (MACE) evaluated at 12 months. Secondary endpoints include notably: angiographic success, Target Lesion Revascularization (TLR), Target Vessel Revascularization (TVR) and stent thrombosis at 12 months' post-procedure. The patient clinical status is evaluated at 12 months by phone call or a visit at the hospital.

RESULTS

Patients' inclusion started in May 2015 and to date 352 patients were enrolled. The 12 months' clinical follow-up results are available for 240 patients. A patient had a cardiac arrest 4 months after the index procedure. Angiographic control for this patient revealed a good result of the previously implanted Amazonia SIR stents (3). The event did not seem to be related to the study device. To date, no other major adverse cardiac event related or not to the study device was reported.

A clinical report will be performed after all patients reached the 12 months' clinical follow-up.

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