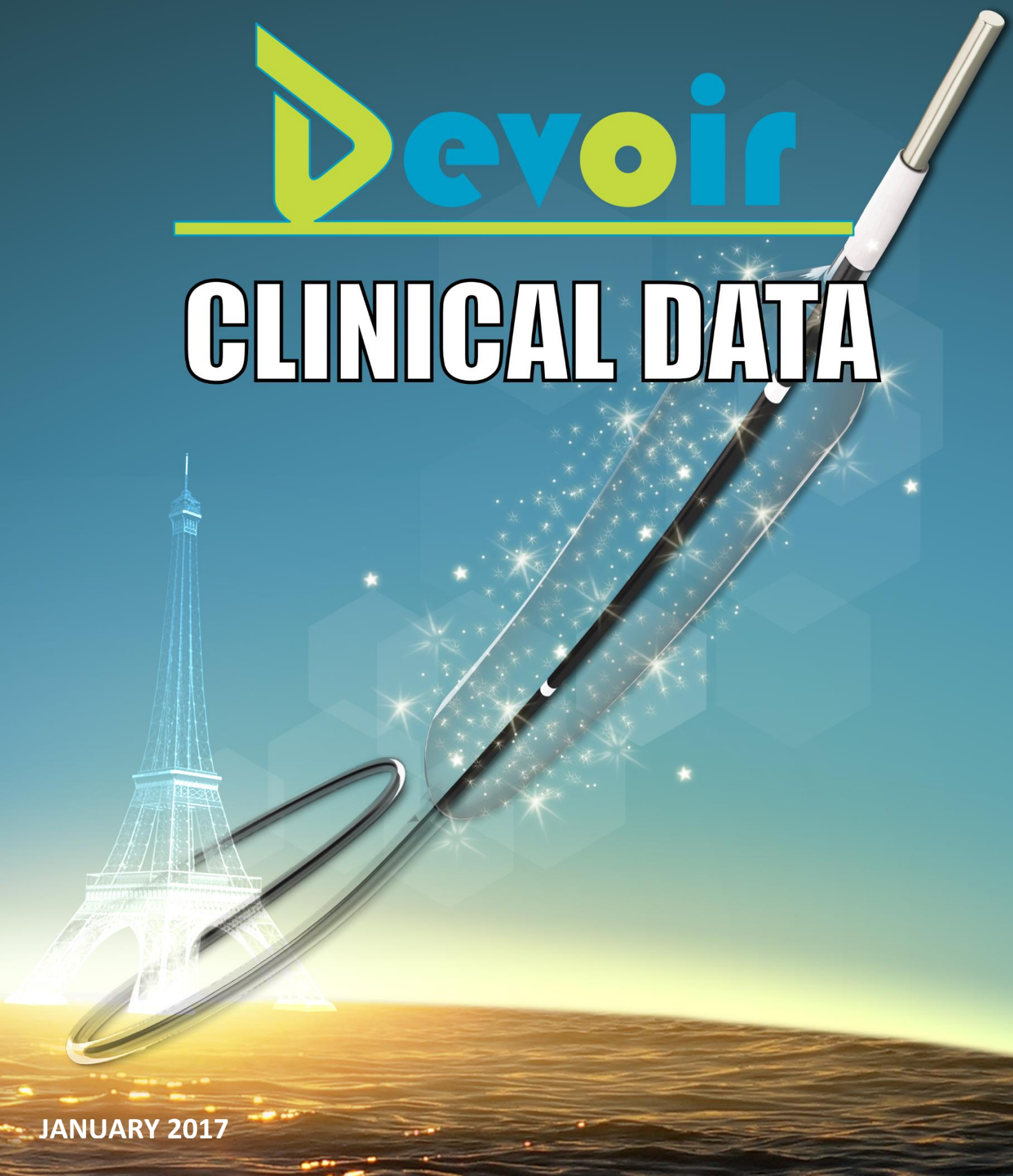
MINVASYS

Devoir

CLINICAL DATA



JANUARY 2017

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1 INTRODUCTION

The use of percutaneous balloon angioplasty to recanalize narrowed coronary arteries and endovascular vessels revolutionized revascularization. However, elastic recoil and restenosis caused by cellular proliferation are major drawbacks of angioplasty. Intracoronary stenting with bare-metal stents (BMS), which could tackle dissections and eliminate elastic recoil, became the next mode of intervention but was limited by stent thrombosis (ST; which is controlled with antiplatelets therapy) and increased neointimal hyperplasia, leading to In-Stent Restenosis (ISR). Drug-eluting stents (DES) significantly attenuate the cellularity and reduce the need for repeat revascularization by reducing restenosis rates to single-digit levels. However, late stent thrombosis, dependency on prolonged dual antiplatelet therapy and continued restenosis led to a quest for new treatment modalities, such as the local delivery of drugs via non-stent based platforms.

In the past years, Drug-Coated Balloons (DCB) have emerged as a potential alternative to reduce in-stent neointimal formation. DCB maintains the antiproliferative properties of DES but without the limitations of DES.

Non-stent-based local drug delivery and particularly using a DCB can dramatically fulfill the goal of DES without duplicating the issues encountered with this technology. It could be of special interest for high-risk restenotic lesions such as small vessel, bifurcation or ISR lesions. The potential advantages of non-stent-based local drug delivery are numerous [1] [2]:

- It allows homogeneous drug transfer to the vessel wall and not only to the areas directly covered by the stent strut, with the potential for enhancing the efficacy of the drug to the artery.
- The drug concentrations at the vessel wall will be the highest at the time of injury when the neointimal process is the most vigorous. Afterward, the absence of drug in the arterial wall may help to better re-endothelialize the stent (if used) and limit the risk for late stent thrombosis.
- The absence of polymer shall decrease the stimulus of chronic inflammation and the trigger for late thrombosis.
- The absence of a stent allows for respect of the original anatomy of the arteries, notably in case of bifurcation or small vessels, leaving no stent scaffold and diminishing abnormal flow patterns observed with stent implantation.
- Overdependence on antiplatelet therapy shall be limited.

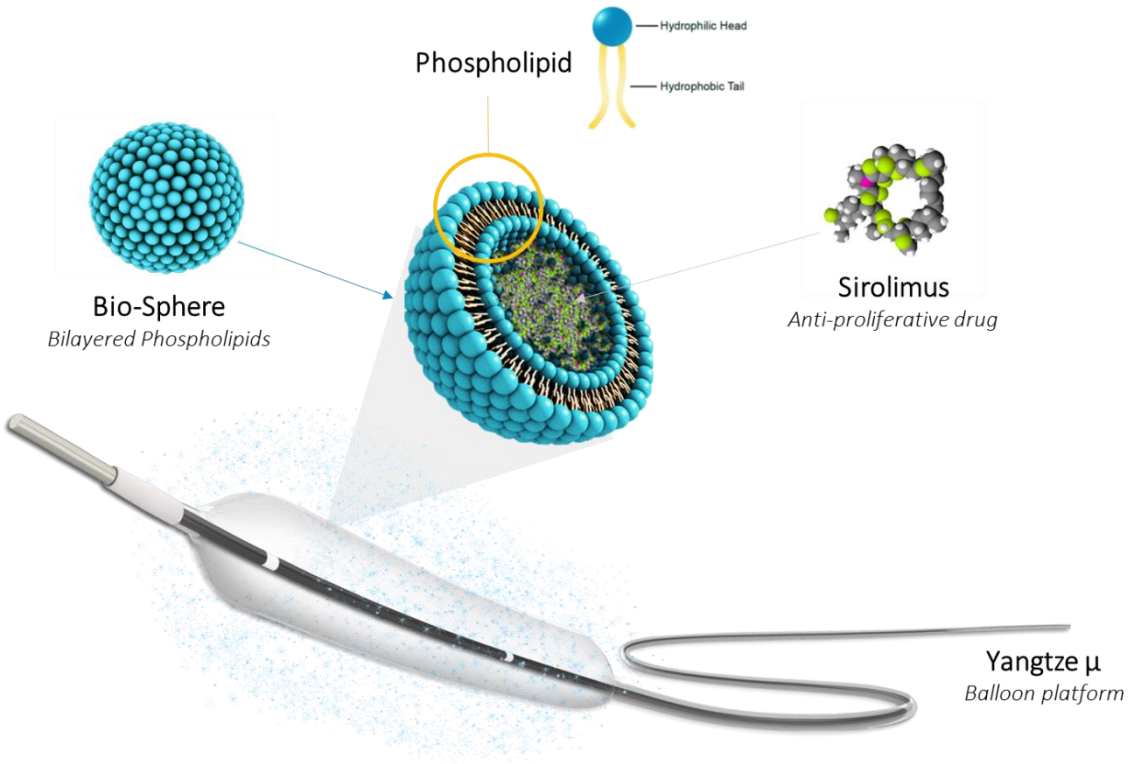
Local drug delivery may also be applied in situations where stents are not used or undesirable, such as in very small vessels, ISR, or for the treatment of the side branch in bifurcation lesions.

To date, various DCB with paclitaxel are on the market and present good clinical results. The sirolimus drug has proven its safety, efficacy and superiority to paclitaxel drug when applied on stent [3] [4]. New DCB with sirolimus drug are currently arriving on the market but clinical data on those devices are still rare. The DEVOIR clinical evaluation represents one of the first in human experience with a sirolimus coated balloon catheter.

2 DEVICE DESCRIPTION

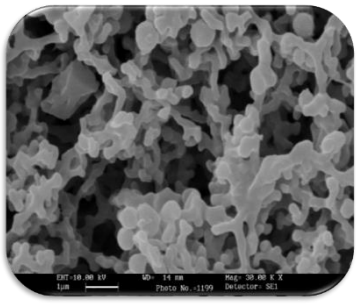
The CE marked DEVOIR sirolimus coated balloon catheter system comprises of a semi-compliant polyamide balloon catheter with low tip profile (0.016") coated with sirolimus drug (concentration: 1.27µg/mm^2 of balloon surface).

Bio-sphere coating technology



The bio-sphere technology features [5]:

- **Cell membrane bio-mimicking carrier**
  - Better compatibility & acceptance in tissue
  - Promotes healing and assists in endothelialization process
- **Small size for higher uptake**
  - Easier & faster transfer into arterial tissue
- **Biosphere Technology**
  - Stabilization of drug particles
  - Assists in long term retention of drug in tissue
  - Protection during transit & transfer
- **Two-steps release**
  - First: Bio-spheres transfer into tissue
  - Second: Drug released from bio-spheres



Anti-proliferative drug – Sirolimus

Sirolimus 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.

Drug carrier – Liposome (phospholipid)

The sirolimus drug is encapsulated into a liposome which is a sphere-shaped vesicle consisting of one or more phospholipid bilayers. Phospholipids are a major component of all cell membranes with a hydrophilic head and a hydrophobic tail. The nature of the carrier (cell membrane bio-mimicking) allows a better compatibility and acceptance in tissue.

Balloon platform – Yangtze μ

The balloon platform is the well-known Yangtze μ PTCA rapid exchange catheter. The balloon catheter is covered with a hydrophilic coating which allow to improve device deliverability and crossability.

DEVOIR AVAILABLE RANGE

LENGTH (mm)	DIAMETER (mm)								
	1.50	2.00	2.25	2.50	2.75	3.00	3.25	3.50	4.00
10	X	X	X	X	X	X	X	X	X
15	X	X	X	X	X	X	X	X	X
20	X	X	X	X	X	X	X	X	X
25	X	X	X	X	X	X	X	X	X
30	X	X	X	X	X	X	X	X	X
35	X	X	X	X	X	X	X	X	X
40	X	X	X	X	X	X	X	X	X

3 DEVOIR SPECIFIC INSTRUCTIONS FOR USE

SPECIFIC STORAGE

Due to the sirolimus drug coating, DEVOIR needs SPECIFIC STORAGES CONDITIONS:

1. Stored in temperature > 8°C and < 25°C
2. Kept dry
3. Kept away from sunlight

DEVOIR PROCEDURE

It is recommended:

1. To pre-dilate the lesion with a PTCA balloon catheter.
2. To inflate the Devoir balloon for a minimum 60s (single inflation) at nominal pressure or two inflations of 30s and 30s at nominal pressure without removing the balloon catheter.

DAPT DURATION

DAPT for a minimum of 3 months and up to 12 months in case of patients with low risk of bleeding.

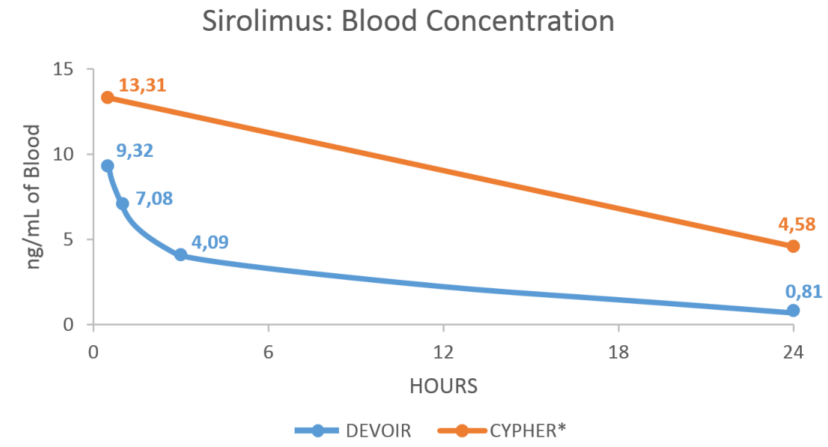
4 DEVOIR PRECLINICAL RESULTS

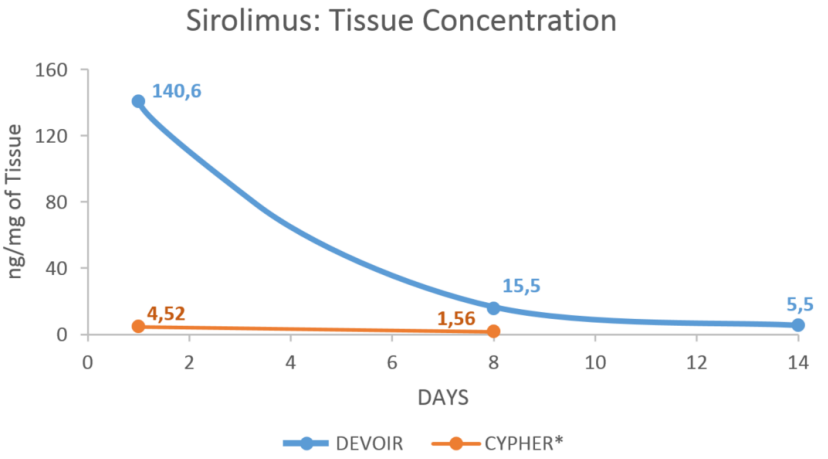
PHARMACOKINETICS STUDY

Method

The study was performed by Dr Renu Virmani (CV PATH INSTITUTE, WASHINGTON DC, USA) with 17 white rabbits (New Zealand) of 5 to 6 months old. The artery location was the iliofemoral and the procedure consisted on sirolimus-coated balloon inflation during 60s with bilateral BMS implantation. Samples were analysed by HPLC-tandem mass spectrometry.

Results





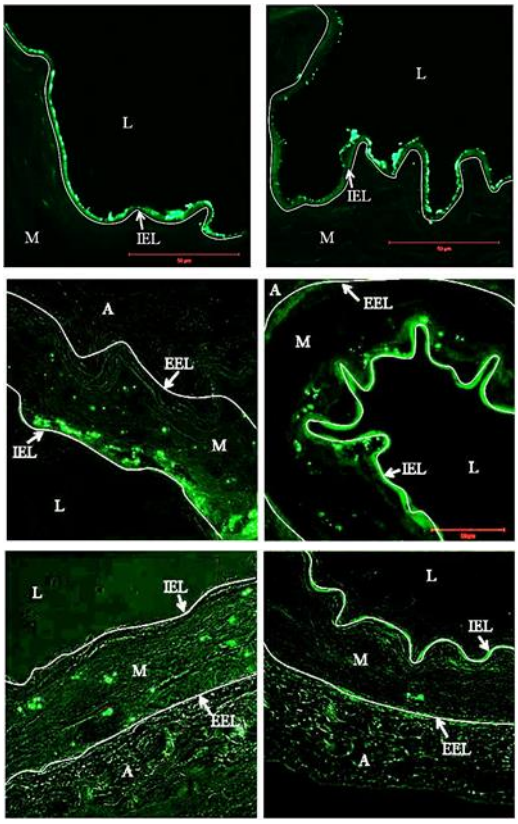
Study results showed **low sirolimus blood levels** and higher level of Sirolimus drug concentrations compared with studies of Sirolimus stent in published literature showing **longer drug retention** in target site [6]. Sirolimus retention in tissue up to 14 days.

DRUG DISTRIBUTION WITHIN ARTERAL TISSUE

Method

The study was performed by Dr Renu Virmani (CV PATH INSTITUTE, WASHINGTON DC, USA). Sirolimus-coated balloons were inflated during 60s in iliac artery of 4 white rabbits (8 iliac arteries). Samples were analysed by confocal microscopy for surface and in-tissue distribution of the bio-sphere.

Results



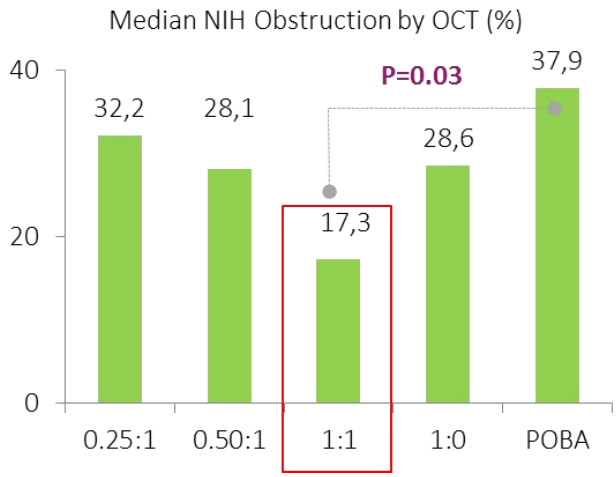
The study results showed **effective drug uptake** with drug retention and absorption **up to 7 days**. The drug was distributed from the intima to the adventitia.

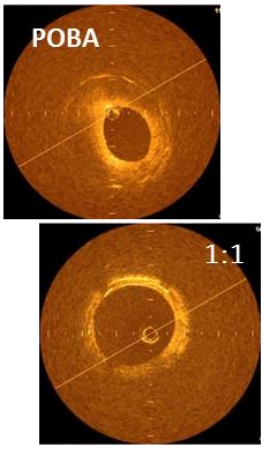
OCT & HISTOLOGIC EVALUATION

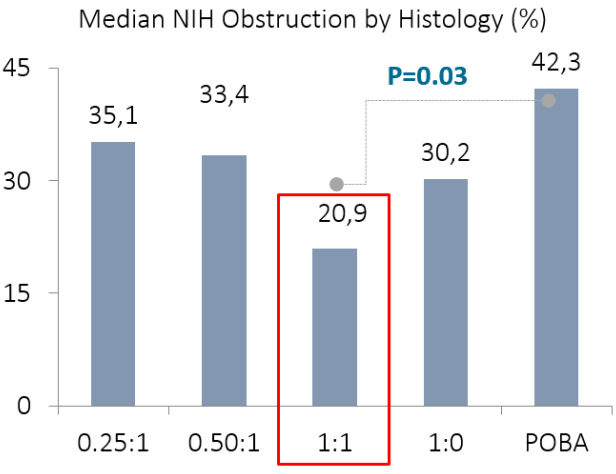
Method

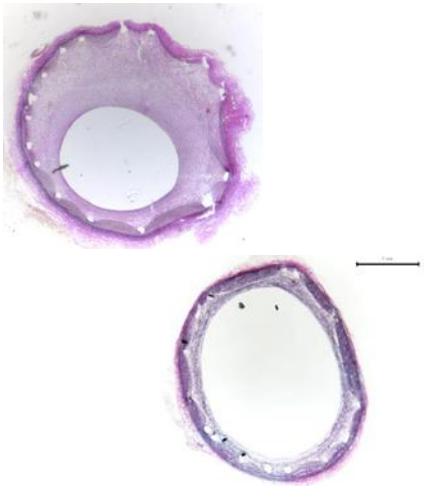
The aim of this evaluation performed by Dr Pedro Lemos (InCOR INSTITUTE) was to test different Excipient:Drug ratio. 14 Domestic pigs were implanted with BMS then treated with a DCB inflation during 60s. The evaluation was done after 28 days with OCT as well as by Light Microscopy of Histology images.

Results









The **1:1 ratio** provides the best NIH reduction with no significant signs of inflammation and no significant fibrin deposition.

5 DEVOIR CLINICAL RESULTS*

AIM

The purpose of the DEVOIR post-market clinical follow-up evaluation is to observe and evaluate the safety and efficacy of the DEVOIR device in the treatment of lesions in native coronary arteries with vessel diameters of 1.50 – 4.00 mm.

METHODS

Study design: Prospective, multicenter clinical registry with real world patients' inclusion.

Primary safety endpoint: MACE rate at 6 months (composite of cardiac death, myocardial infarction and target lesion/vessel revascularization).

Primary efficacy endpoint: Procedural success (technical and angiographic success in the absence of MACE at hospital discharge).

Clinical follow-ups: 1, 6 and 12 months.

Inclusion objective: 1000 patients

To date, 359 patients with 428 lesions were recruited. Patients with in-stent restenosis (ISR) or small vessel diameter indications have been also analyzed apart as a subgroup.

Patients' demographic data are presented hereinafter:

POPULATION	
Patient, n	359
Age, years	59.9±10.5
Male, %	81.3
CLINICAL INDICATION	
Stable angina, %	49.9
Unstable angina, %	31.8
Non-ST elevation MI, %	5.9
ST-elevation MI, %	10.6
RISK FACTORS	
Diabetes, %	46.8
Hypertension, %	47.9
Hyperlipidemia, %	8.4
Family history of CAD, %	3.9

LESIONS CHARACTERISTICS	
Lesion, n	428
Lesion type, % - De novo - Bifurcation - Small vessel - In-stent restenosis	 8.9 1.7 42.9 46.5

**Post-market clinical follow-up evaluation*

RESULTS

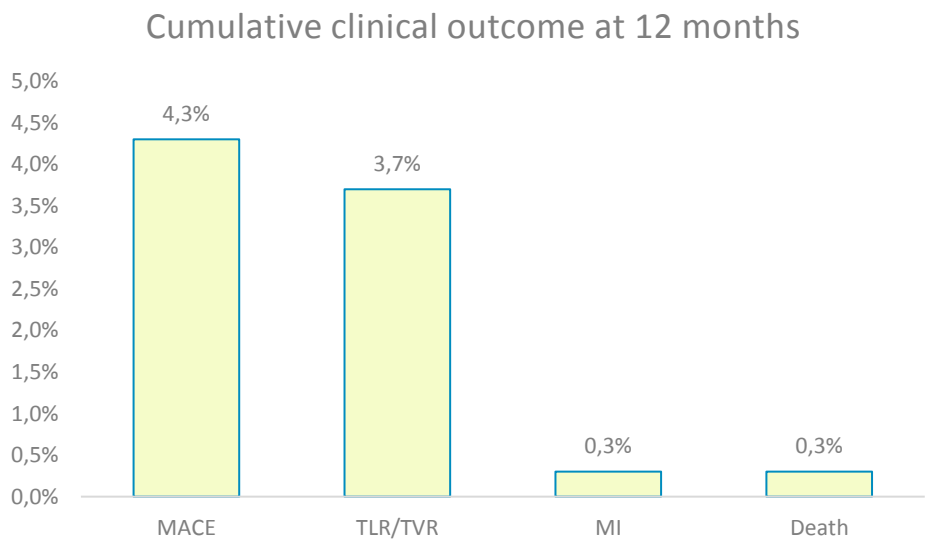
Procedural data

All 428 lesions treated were pre-dilated and 7.0% of patients were treated with a bare-metal stent in combination with the DEVOIR. The mean diameter of the DEVOIR was 2.7mm with a mean total length of 21.8mm. The DEVOIR balloon was inflated with a mean pressure of 11.19 atm during a mean time of 56.14 seconds.

12 months' clinical follow-up results

Patients were clinically followed by phone call or visit at the hospital. To the date of this analysis, 323 patients had completed their 12 months' clinical follow-up.

Results included in the following scheme present outcomes for all patients that achieved their 12 months' follow-up.



IN-STENT RESTENOSIS SUBGROUP ANALYSIS

Methods

167 patients with 180 ISR lesions were included in this registry. Patients' demographic data are presented hereinafter:

POPULATION	
Patient, n	167
Age, years	60.3±9.2
Male, %	79.6
CLINICAL INDICATION	
Stable angina, %	50.6
Unstable angina, %	38.3
Non-ST elevation MI, %	4.2
ST-elevation MI, %	4.8

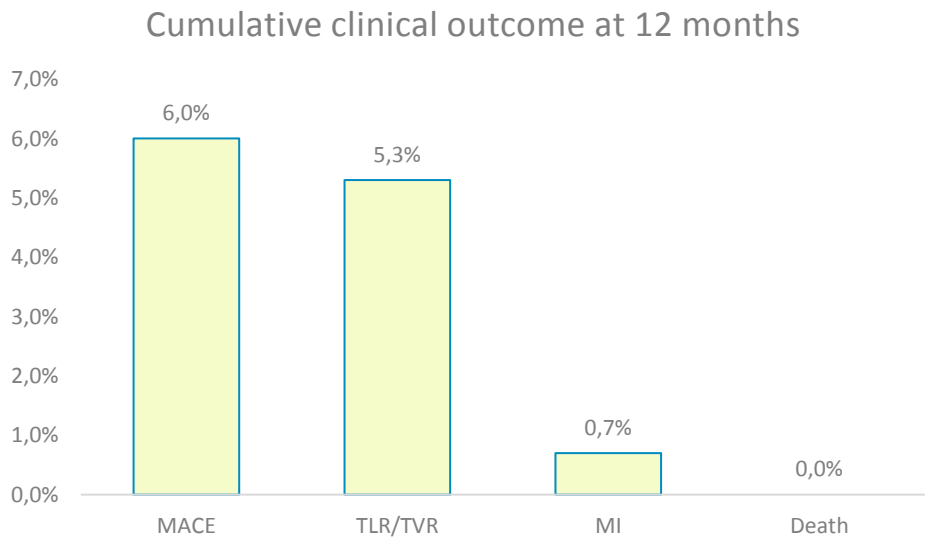
RISK FACTORS	
Diabetes, %	53.9
Hypertension, %	50.9
Family history of CAD, %	5.4
LESIONS CHARACTERISTICS	
Lesion, n	180
ISR classification, % - Diffuse proliferative - Diffuse intra-stent - CTO - Focal	 8.3 18.3 8.3 62.8

Results

12 months' clinical follow-up results

Patients were clinically followed by phone call or visit at the hospital. To the date of this analysis, 150 patients had completed their 12 months' clinical follow-up.

Results included in the following scheme present outcomes for all patients that achieved their 12 months' follow-up.



SMALL VESSEL SUBGROUP ANALYSIS

Methods

145 patients with 168 small vessel diameter lesions were included in this registry. Patients' demographic data are presented hereinafter:

POPULATION	
Patient, n	154
Age, years	58.7±11.4
Male, %	82.5
CLINICAL INDICATION	
Stable angina, %	46.1
Unstable angina, %	25.3
Non-ST elevation MI, %	8.4
ST-elevation MI, %	17.5

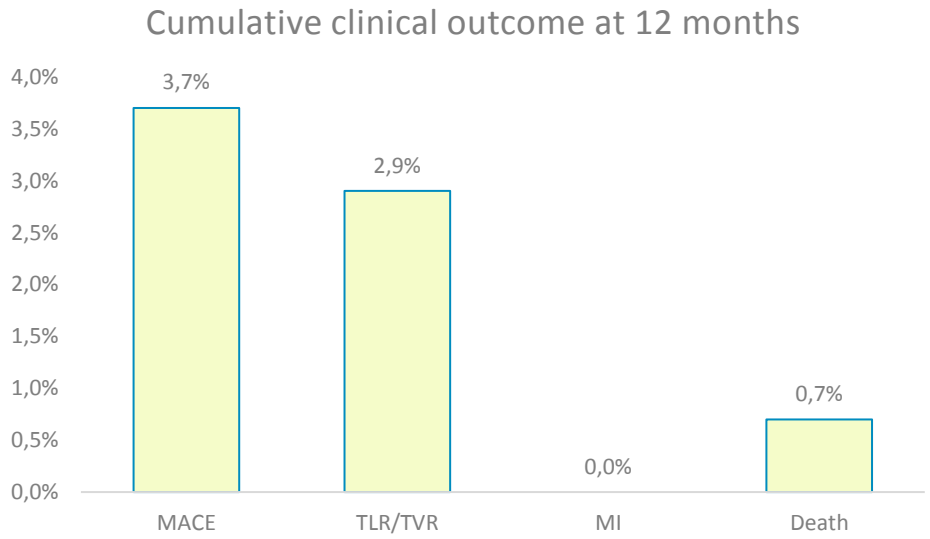
RISK FACTORS	
Diabetes, %	42.2
Hypertension, %	45.5
Hyperlipidemia, %	3.9
Family history of CAD, %	2.6

Results

12 months' clinical follow-up results

Patients were clinically followed by phone call or visit at the hospital. To the date of this analysis, 137 patients had completed their 12 months' clinical follow-up.

Results included in the following scheme present outcomes for all patients that achieved their 12 months' follow-up.



CONCLUSION

Based on the preliminary results, the DEVOIR for the treatment of coronary artery disease including in-stent restenosis and small vessel diameter lesions is safe and efficient. Indeed, interim analysis indicated low rates of events with only 4.3% of cumulative MACE in patients who reached 12 months' post-procedure follow-up. The clinical results in the ISR and small vessel diameter lesions subgroups were similar.

A thousand patients are expected to be enrolled in this DEVOIR clinical evaluation. The final results of this large cohort of patient in a real-world population should confirm the safety and efficacy of the DEVOIR sirolimus coated balloon catheter demonstrated through this preliminary report.

6 REFERENCES

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