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Real-world experience with a novel biodegradable polymer sirolimus-eluting stent: twelve-month results of the BIOFLOW-III registry

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KEYWORDS

- biodegradable polymer
- bioresorbable stent
- coronary artery disease
- drug-eluting stent
- PLLA
- sirolimus

Abstract

Aims: We aimed to assess the safety and performance of a novel sirolimus-eluting stent with biodegradable polymer under real-world conditions.

Methods and results: This prospective, multicentre, observational, all-comers registry enrolled 1,356 patients. The primary endpoint was target lesion failure at 12 months: it occurred in 5.1% (95% CI: 4.0-6.4) of patients in the overall population and in 7.7% (95% CI: 5.5-10.9), 5.8% (95% CI: 4.2-8.1), 1.8% (95% CI: 0.2-11.8) and 7.2% (95% CI: 5.1-10.0) of patients with diabetes mellitus, small vessels, chronic total occlusion and acute myocardial infarction, respectively.

Conclusions: This novel stent platform demonstrated good clinical outcomes in an all-comers population, even in predefined high-risk groups. ClinialTrials.gov identifier: NCT01553526

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Introduction

Hybrid drug-eluting stents (DES) provide temporary drug exposure with subsequent degradation of the polymer, leaving a bare metal stent in the vessel, and hence address concerns associated with permanent polymer stents such as suboptimal polymer compatibility, delayed stent endothelialisation and late stent thrombosis[1-3]. The Orsiro (Biotronik AG, Bülach, Switzerland) hybrid DES has shown promising results in the BIOFLOW-I[1] and BIOFLOW-II[2] studies. We aimed to assess whether the good results of these selected patient populations can be replicated in unselected patients under real-world conditions and in predefined high-risk groups.

Methods and results

The BIOFLOW-III registry is a prospective, non-randomised, multicentre, observational all-comers registry to evaluate the safety and performance of the Orsiro DES in a large series of patients under real-world conditions with treatment according to standard of care and follow-up assessments up to 60 months. The Orsiro DES has been previously described[1]. In brief, it is made of a cobalt-chromium alloy which is covered by a thin layer of amorphous silicon carbide. The biodegradable polymer used as a carrier material for sirolimus is poly-L-lactic acid (PLLA).

The registry was conducted according to the Declaration of Helsinki and ISO 14155:2011 and approved by all relevant regional ethical review boards. All patients provided informed consent, 25% of randomly chosen subjects were monitored for endpoint-related data, and all serious adverse events were adjudicated by an independent clinical events committee. Data are presented using descriptive statistical methods. Predefined subgroups were compared using Fisher's exact test, the chi-squared and the Student's t-test. A Kaplan-Meier estimator, log-rank test and Cox proportional hazards model were used for survival analysis.

From August 2011 until March 2012, 1,356 patients with 1,738 lesions were enrolled at 43 sites in 14 countries **(Figure 1)**. The baseline patient and lesion characteristics are shown in **Table 1** and **Table 2**. Lesions were predominantly located in the left anterior descending artery (40%), followed by the right coronary artery (32%), the circumflex artery (22%), coronary artery bypass graft (CABG) (3%), left main (2%) and the anterolateral branch (1%). Predilatation was conducted in 65.9% of the treated lesions, and post-dilatation in 25.3%. Clinical device success and procedure success were achieved in 98.8% and 98.2% of the patients, respectively.

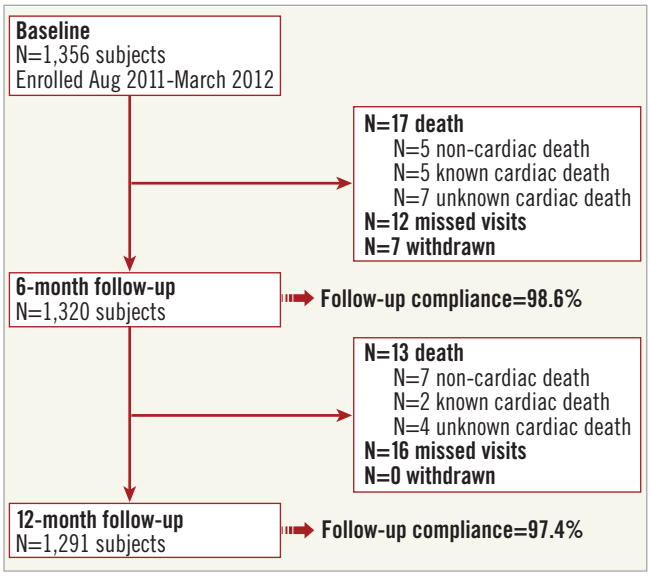


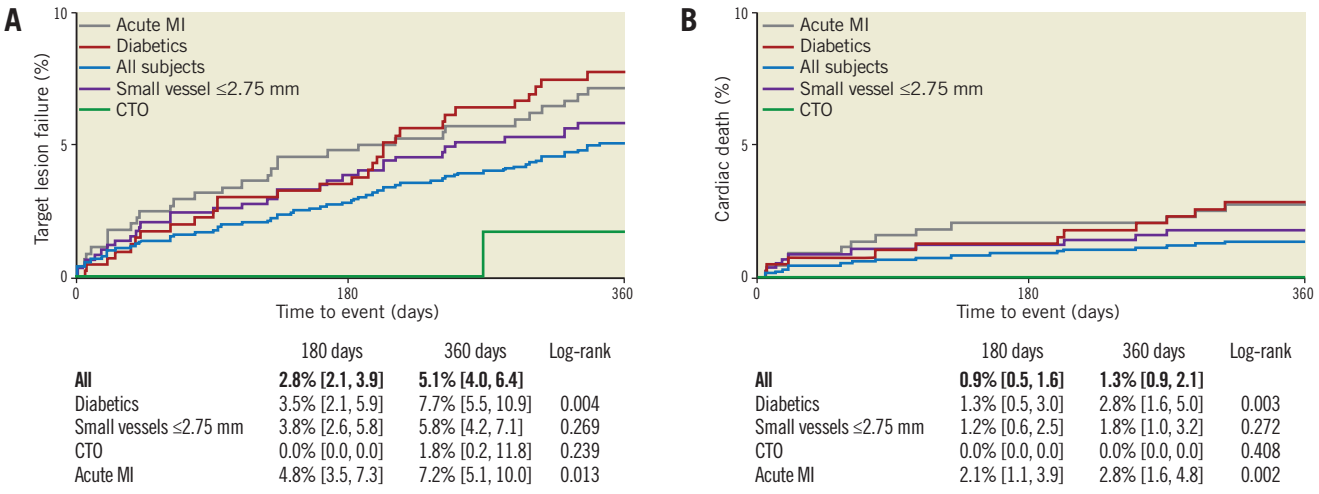
Figure 1. *Flow chart of patients from baseline to 12-month follow-up.*

The primary endpoint of the study, target lesion failure (TLF), a composite of cardiac death, target vessel myocardial infarction (MI), CABG and clinically driven target lesion revascularisation (TLR) at 12 months, was 5.1% (95% CI: 4.0-6.4) **(Figure 2A)**. As displayed in **Figure 3**, diabetes mellitus, renal insufficiency and NSTEMI were associated with an increased TLF rate (HR 2.00

Table 1. Baseline patient characteristics.

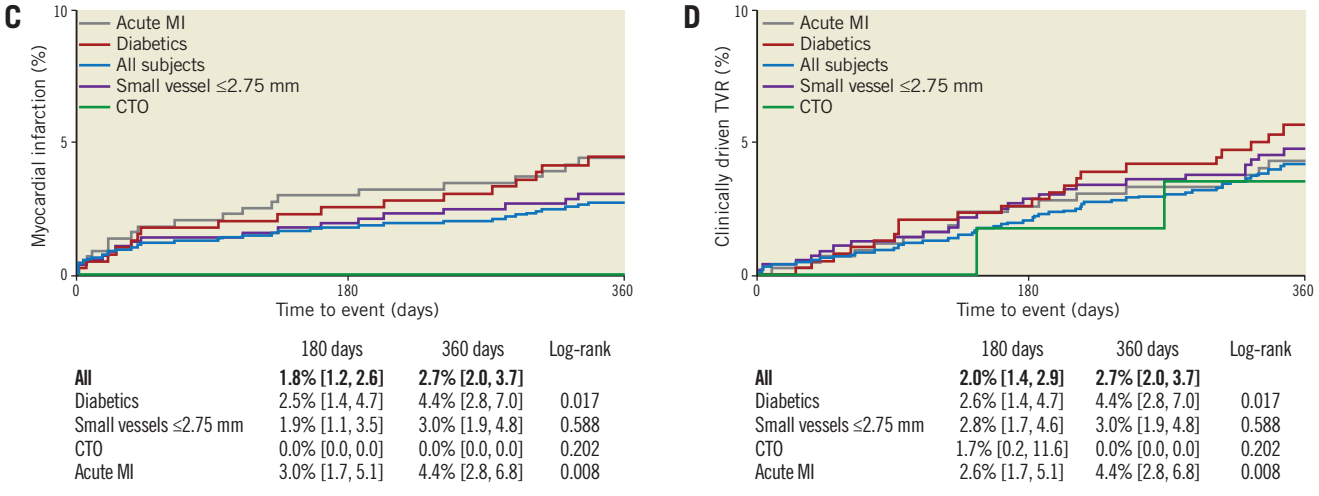
	Overall N=1,356	Diabetics N=402	*p*-value	Vessels ≤2.75 mm N=575	*p*-value	CTO N=58	*p*-value	Acute MI N=442	*p*-value
Age in years	66.1±10.7	68.6±9.8	<0.001	67.2±10.5	0.001	64.7±10.1	0.321	64.9±11.8	0.003
Male	971/71.6	288/71.6	0.977	411/71.5	0.980	46/79.3	0.175	294/66.5	0.004
Hypertension	1,029/75.9	352/87.6	<0.001	454/79.0	0.040	47/81.0	0.391	293/66.3	<0.001
Hypercholesterolaemia	815/60.1	256/63.7	0.088	351/61.0	0.505	35/60.3	0.936	222/50.2	<0.001
Smoking	741/54.6	195/48.5	0.002	293/51.0	0.012	32/55.2	0.875	257/58.1	0.077
Diabetes mellitus	402/29.6	402/100.0	n/a	188/32.7	0.038	16/27.6	0.867	114/25.8	0.033
Insulin-dependent	137/34.1	137/34.1		75/39.9		6/37.5		44/38.6	
Non-insulin-dependent	265/65.9	265/65.9		113/60.1		10/62.5		70/61.4	
History of MI	376/27.7	127/31.6	0.039	164/28.5	0.573	16/27.6	0.991	87/19.7	n/a
Stable angina	641/47.3	203/50.5	0.127	279/48.5	0.282	34/58.6	0.107	0/0	n/a
Previous PCI	537/39.6	182/45.3	0.006	233/40.5	0.486	16/27.6	0.046	95/21.5	<0.001

Data shown as mean±SD and n/%. CTO: chronic total occlusion; MI: myocardial infarction; RVD: reference vessel diameter



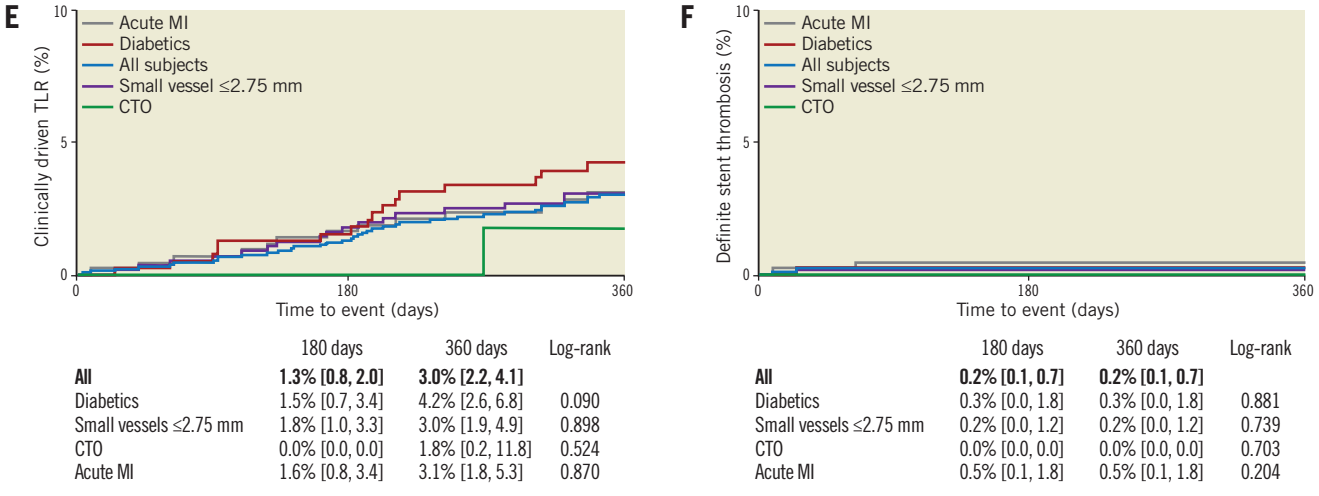
	180 days	360 days	Log-rank
All	**2.8% [2.1, 3.9]**	**5.1% [4.0, 6.4]**	
Diabetics	3.5% [2.1, 5.9]	7.7% [5.5, 10.9]	0.004
Small vessels ≤2.75 mm	3.8% [2.6, 5.8]	5.8% [4.2, 7.1]	0.269
CTO	0.0% [0.0, 0.0]	1.8% [0.2, 11.8]	0.239
Acute MI	4.8% [3.5, 7.3]	7.2% [5.1, 10.0]	0.013

	180 days	360 days	Log-rank
All	**0.9% [0.5, 1.6]**	**1.3% [0.9, 2.1]**	
Diabetics	1.3% [0.5, 3.0]	2.8% [1.6, 5.0]	0.003
Small vessels ≤2.75 mm	1.2% [0.6, 2.5]	1.8% [1.0, 3.2]	0.272
CTO	0.0% [0.0, 0.0]	0.0% [0.0, 0.0]	0.408
Acute MI	2.1% [1.1, 3.9]	2.8% [1.6, 4.8]	0.002



	180 days	360 days	Log-rank
All	**1.8% [1.2, 2.6]**	**2.7% [2.0, 3.7]**	
Diabetics	2.5% [1.4, 4.7]	4.4% [2.8, 7.0]	0.017
Small vessels ≤2.75 mm	1.9% [1.1, 3.5]	3.0% [1.9, 4.8]	0.588
CTO	0.0% [0.0, 0.0]	0.0% [0.0, 0.0]	0.202
Acute MI	3.0% [1.7, 5.1]	4.4% [2.8, 6.8]	0.008

	180 days	360 days	Log-rank
All	**2.0% [1.4, 2.9]**	**2.7% [2.0, 3.7]**	
Diabetics	2.6% [1.4, 4.7]	4.4% [2.8, 7.0]	0.017
Small vessels ≤2.75 mm	2.8% [1.7, 4.6]	3.0% [1.9, 4.8]	0.588
CTO	1.7% [0.2, 11.6]	0.0% [0.0, 0.0]	0.202
Acute MI	2.6% [1.7, 5.1]	4.4% [2.8, 6.8]	0.008



	180 days	360 days	Log-rank
All	**1.3% [0.8, 2.0]**	**3.0% [2.2, 4.1]**	
Diabetics	1.5% [0.7, 3.4]	4.2% [2.6, 6.8]	0.090
Small vessels ≤2.75 mm	1.8% [1.0, 3.3]	3.0% [1.9, 4.9]	0.898
CTO	0.0% [0.0, 0.0]	1.8% [0.2, 11.8]	0.524
Acute MI	1.6% [0.8, 3.4]	3.1% [1.8, 5.3]	0.870

	180 days	360 days	Log-rank
All	**0.2% [0.1, 0.7]**	**0.2% [0.1, 0.7]**	
Diabetics	0.3% [0.0, 1.8]	0.3% [0.0, 1.8]	0.881
Small vessels ≤2.75 mm	0.2% [0.0, 1.2]	0.2% [0.0, 1.2]	0.739
CTO	0.0% [0.0, 0.0]	0.0% [0.0, 0.0]	0.703
Acute MI	0.5% [0.1, 1.8]	0.5% [0.1, 1.8]	0.204

Figure 2. *Kaplan-Meier event estimates. Kaplan-Meier event estimates for: A) target lesion failure, B) cardiac death, C) myocardial infarction, D) clinically driven target vessel revascularisation, E) clinically driven target lesion revascularisation, and F) definite stent thrombosis. CTO: chronic total occlusion; MI: myocardial infarction*

[95% CI: 1.23-3.23], HR 1.89 [95% CI: 1.03-3.46], and HR 2.09 [95% CI: 1.27-3.45], respectively). Kaplan-Meier estimates for the individual TLF components, target vessel revascularisation and definite stent thrombosis are provided in **Figure 2B-Figure 2F**.

Discussion

Despite a high proportion of high-risk patients, the BIOFLOW-III registry had slightly better outcomes than those observed in the BIOFLOW-I[1] and BIOFLOW-II[2] studies (12-month composite of

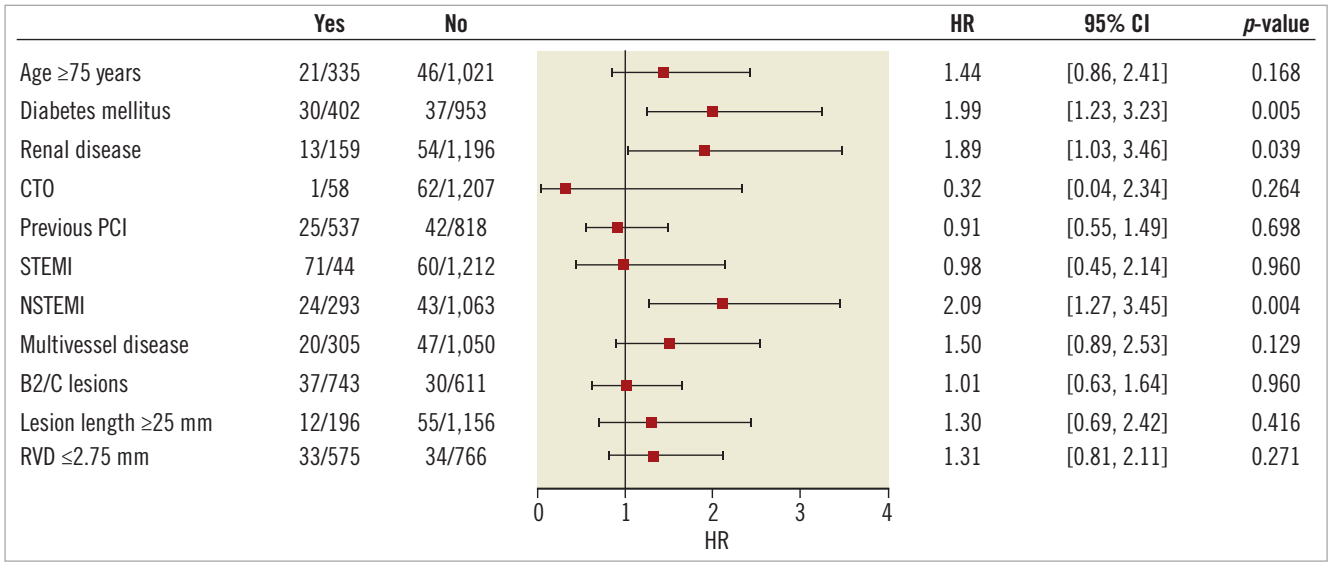


Figure 3. *Cox proportional hazards for target lesion failure. Cox proportional hazards for target lesion failure with Wald test and Wald confidence limits for the hazard ratio. The squares indicate the hazard ratios and the horizontal lines indicate 95% confidence intervals. CTO: chronic total occlusion; HR: hazard ratio; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; RVD: reference vessel diameter; STEMI: ST-elevation myocardial infarction; TLF: target lesion failure*

cardiac death, target vessel MI, CABG and TLR of 5.1% compared to 10.0%[1] and 6.5%[2]). The outcomes of BIOFLOW-III also compare well with those of other biodegradable polymer stents such as BioMatrix™ (Biosensors Inc., Newport Beach, CA, USA) and Nobori® (Terumo Corporation, Tokyo, Japan). At 12 months, cardiac death was 1.3% for Orsiro compared to 0.8%-1.2% for Nobori[3-5] and 2.1% for BioMatrix[6], MI was 2.7% versus 1.5%-2.8%[3-5] and 5.9%[6], clinically driven TLR was 3.0% compared to 2.2%-3.3%[3-5] and 6.0%[6], and definite stent thrombosis was 0.2% compared to 0.7%[3,5] and 2.0%[6]. Furthermore, the data compare well with the outcomes of a recent meta-analysis including 60 trials with DES[7].

In the predefined groups, patients with diabetes and patients with acute MI had significantly higher TLF, cardiac death and MI rates. There was no such difference for patients with small vessels. Correspondingly, Cox proportional hazards for TLF identified diabetes mellitus, renal disease and NSTEMI as influencing factors.

To the best of our knowledge, BIOFLOW-III is the first trial to assess clinical outcomes of biodegradable polymer stents in patients with CTO. The TLF rate of 1.8% at 12 months was good and was attributed to TLR only. However, only 58 patients were enrolled in the CTO group, hence results have to be interpreted with caution and would need to be confirmed in a larger series of patients. Notably, the registry was not powered to detect differences in subgroups, hence the results of the subgroup analysis must be regarded as hypothesis-generating only.

Conclusions

The low 12-month TLF rate of 5.1% and definite stent thrombosis rate of 0.2% in this all-comers setting imply safety and effectiveness of the Orsiro DES with biodegradable polymer. Low event rates were also confirmed in subgroups of diabetics, small vessels, CTO and acute MI.

Table 2. Baseline lesion characteristics.

	Overall N=1,738	Diabetics N=517	*p*-value	Vessels ≤2.75 mm N=828	*p*-value	CTO N=83	*p*-value	Acute MI N=551	*p*-value
B2/C type lesions	905/52.1	253/48.9	0.085	413/49.9	0.040	67/80.7	<0.001	318/57.7	0.001
Bifurcation	282/16.2	68/13.2	0.023	145/17.5	0.175	22/26.5	0.011	89/16.2	0.980
Moderate calcification	411/23.6	141/27.3	0.025	216/26.1	0.031	20/24.1	0.880	121/22.0	0.317
Severe calcification	122/7.0	41/7.9	0.353	45/5.4	0.010	10/12.0	0.091	29/5.3	0.058
RVD (mm)	3.0±0.4	3.0±0.4	0.402	2.7±0.3	<0.001	2.9±0.5	0.133	3.0±0.4	0.038
Lesion lengths (mm)	15.8±9.1	15.4±9.3	0.288	15.2±8.4	0.015	21.8±12.9	<0.001	15.3±7.6	0.131
Diameter stenosis (%)	86.3±11.1	85.9±11.2	0.412	86.3±10.9	0.982	95±11.1	<0.001	90.4±10.1	<0.001

Data shown as mean±SD and n/%. CTO: chronic total occlusion; MI: myocardial infarction; RVD: reference vessel diameter

Impact on daily practice

Drug-eluting stents with biodegradable polymer are novel devices which should address concerns asociated with permanent polymer stents. BIOFLOW-III shows, in a large patient population of more than 1,300 patients, that a novel DES with biodegradable polymer can be safely applied in an all-comer population, even in high-risk populations such as those with diabetes mellitus, small vessels, chronic total occlusions and acute myocardial infarction.

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Conflict of interest statement

J. Waltenberger and A. Erglis have received lecture honoraria and consulting fees from Biotronik. O. Fröbert has received consulting fees, G. Richardt and S. Hofmann have received lecture honoraria, and M. Winkens has received research grants from Biotronik. The other authors have no conflicts of interest to declare.

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