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Original Article

Early and aggressive ISR with a polymer- and carrier-free drug-coated stent system

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ABSTRACT

The LEADERS FREE trial concluded that the polymer free drug-coated BioFreedom™ stent appeared to be both safer and more effective than bare-metal stents (BMS) with an ISR rate comparable to traditional DES without the need for prolonged DAPT. We implanted 45 BioFreedom™ stents in 34 patients over a 4-month period. 4 patients represented early (106–238 days after the implant procedure) with angina symptoms and severe ISR was detected in all patients. The rate of severe and early ISR detected in our patient population of 11.8% is comparable to that of traditional BMS. Further studies are warranted.

1. Introduction

The LEADERS FREE trial concluded that the polymer free drug-coated BioFreedom™ stent (DCS) appeared to be both safer and more effective than bare-metal stents (BMS) making it an interesting option in patients at high risk of bleeding in view of the shorter duration of dual antiplatelet therapy required.[1] The LEADERS trial was sponsored by Biosensors Europe (Morges, Switzerland). The reported clinically-driven target lesion revascularization rate at 1 year was only 5.1% for the DCS compared to 9.8% for the BMS.[1] The higher rate of in-stent restenosis (ISR) is one of the major disadvantages of BMS compared to drug-eluting stents (DES) but the LEADERS FREE trial for the first time showed an ISR rate for a stent that was comparable to traditional DES but did not require 12 months of dual antiplatelet therapy.[1–3]

2. Methods

The study is a small case series comprising a review of patients who were implanted with BioFreedom™ stents over a 4-month period from 29.04.2015 until 29.08.2015. On May 1st 2016, we retrospectively reviewed all patients that were implanted with a Biofreedom stent during that 4-month period. We analysed our angiogram database, whether patients underwent further angioplasty procedures following the Biofreedom implant. All angiograms were reviewed. Patients who did not undergo additional angioplasties were called up and questioned about the presence of ischaemic symptoms or whether the patient underwent procedures elsewhere.

3. Results

45 BioFreedom™ stents were implanted in 34 patients during the study period. The mean follow-up period was 322 days (minimum 247 days; maximum 368 days). We found, that 4 patients had to be re-studied when they presented with angina, an average of 186 days after the index procedure (106–238 days). In addition, early but asymptomatic ISR was noted in an additional patient during a staged procedure 36 days after implantation. All patients with severe ISR were of Indian ethnicity and diabetics. All other patients denied ischaemic symptoms when followed up. None of the patients underwent angiography in other hospitals. 1 patient had died due to a haematological condition. Patient characteristics and description of the procedures performed are outlined in Tables 1 and 2, respectively.

By just focusing on the 4 patients with severe ISR relatively early after stent implantation, we have to report a rate of severe ISR requiring re-intervention of 11.8%. The ISR seems to occur very early and appears to be aggressive. All 4 patients described had almost subtotal occlusion of their stents. Coronary angiogram images illustrating the initial stenosis and the result of the Biofreedom stenting procedure ("index procedure") and the observed ISR during relook angiogram are shown in Fig. 1.

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Table 1
Patient characteristics.

	Patients without ISR	Patients with ISR	Total study group
Number of patients	29	5	34
Age			
Mean	60 years	60 years	60 years
Range	25–83 years	54 –64 years	25–83 years
Gender			
Female	4	1	5 (15%)
Male	25	4	29 (85%)
Ethnicity			
Malay	13	0	13 (38%)
Indian	9	5	14 (41%)
Chinese	7	0	7 (21%)
Risk factors			
Diabetes mellitus	15	5	20 (59%)
Hypertension	23	5	28 (82%)
Hyperlipidaemia	20	3	23 (68%)
Family history CAD	5	1	6 (18%)
Previous angioplasty	6	0	6 (18%)
Current smoker	9	1	10 (29%)
Ex-smoker	5	1	6 (18%)
Never smoked	15	3	18 (53%)
Indication for angiogram			
STEMI	11	0	11 (32%)
NSTEMI	3	0	3 (9%)
Angina	13	4	17 (50%)
Exertional dyspnoea	2	1	3 (9%)
Patient on DAPT post procedure	29	5	34 (100%)
Type of DAPT			
Aspirin/plavix	26	5	31 (91%)
Aspirin/ticagrelor	3	0	3 (9%)

ISR – in-stent restenosis; CAD – coronary artery disease; STEMI – ST elevation myocardial infarction; NSTEMI – non-ST elevation myocardial infarction; DAPT – dual antiplatelet therapy.

Table 2
Procedure description.

Pt. no.	Index procedure				Indication for re-look	Time since index procedure	Re-look procedure findings/ Mehran classification ISR[4]	ISR treatment
	Index lesion/ lesion type[5]	Pre-dilation	Stent specification	NC ballooning				
1	95% stenosis mid-LAD Type C	Sprinter 2 × 15 @10 bar	Biofreedom 2.5 × 33 @14 bar	Not done	Angina	106 d	Type IV ISR (total in-stent occlusion)	Balloon Euphora 2.5 × 15 @14 bar Promus 3.0 × 20 @12 bar
2	80% stenosis LCX Type A	Not done	Biofreedom 3 × 28 @8 bar	Not done	Staged PCI to RCA	36 d	Type I-C (focal ISR) Non-obstructive	No treatment required
3	95% stenosis PDA Type A	Tazuna 1.5 × 15 @6 bar	Biofreedom 2.75 × 14 @ 10 bar	Hiryu 2.75 × 10 @14 bar IVUS guided	Angina	196 d	Type I-C (focal ISR) 80% ISR mid stent	Ultimaster 3.0 × 15@16 bar IVUS guided
4	90% stenosis proximal RCA Type A	Not done	Biofreedom 3.5 × 24 @12 bar	Sapphire NC 3.5 × 15 @16 bar	Angina	204 d	Type I-D (multifocal ISR) Subtotal ISR, exceeding the proximal stent edge	Balloon Accuforce 2.5 × 15@18 bar Ultimaster 3.5 × 18@12 bar IVUS guided
5	80% stenosis proximal LAD Type C	Not done	Biofreedom 2.5 × 28 @12 bar	Hiryu 2.75 × 15 @18 bar	Angina	238 d	Type I-D (multifocal ISR) Subtotal ISR, exceeding the proximal stent edge	NC Balloon Hiryu 2.75 × 15@10 bar Synergy 2.75 × 38 @11 bar NC balloon Accuforce 3.0 × 15@20 bar

ISR – in-stent restenosis; d – days; RCA – right coronary artery; LAD – left anterior descending artery; LCX – left circumflex artery; PDA – posterior descending artery; PCI – percutaneous coronary intervention; NC – non-compliant; IVUS – intravascular ultrasound.

4. Discussion

The superiority of drug-eluting stents (DES) over bare-metal stents with regards to restenosis and cardiovascular outcome is well proven.[2,3,6] The only remaining advantage of bare metal stents is the shorter dual anti-platelet therapy (DAPT) duration; an important issue for patients at high bleeding risk or patients with the need to undergo non-cardiac surgery.[7,8]

Prior to BioFreedom™, BMS were often preferred in these situations.[9] The polymer coating of a classic DES serves to attach and release the anti-inflammatory and antiproliferative drug in a sustained way. However, because of concerns that the polymer

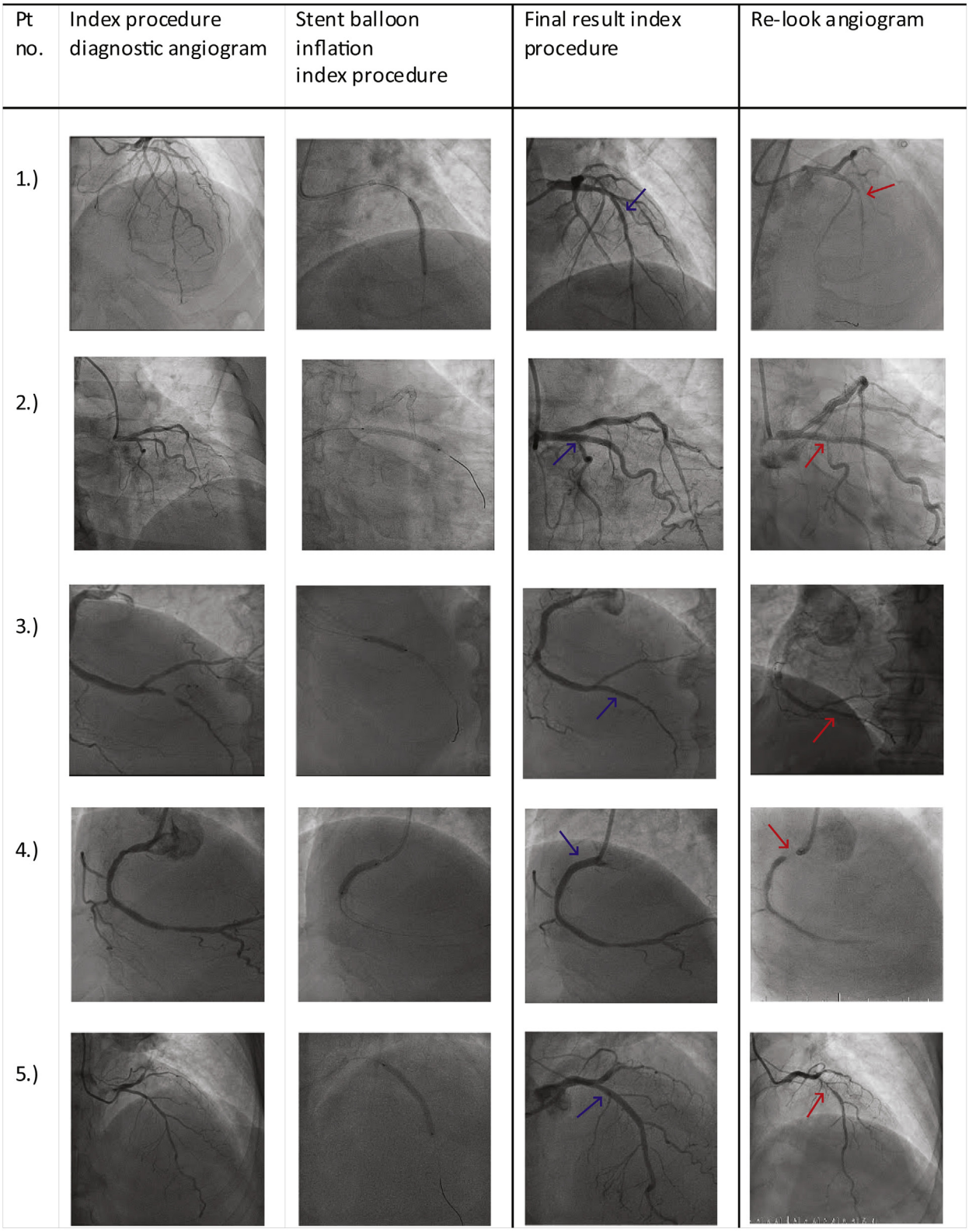

Fig. 1. Angiogram images from index procedure with placement of BioFreedom™ stent. Blue arrows indicate result of the index procedure. Red arrows indicate restenosis on re-look angiogram. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

coating itself can be associated with adverse events like late stent thrombosis, several strategies have been adopted to eliminate the polymeric coating.[10] In the case of BioFreedom™, the micro-structured abluminal surface promotes attachment of the anti-proliferative drug Biolimus A9™. On the BioFreedom stent, the BA9™ is transferred rapidly over a period of approximately 50 h from the stent into the vessel wall.[11] Thereafter, the Biofreedom stent is considered to behave essentially like a BMS combining the advantages of both DES and BMS: delivering an anti-restenotic therapy with Biolimus A9™, combined with a shortened DAPT

regime. Data from the LEADERS FREE trial seems to support this theory with a reported TVR rate of only 5.1% at 1 year.[1] Our observations were however very different. It appears that the absence of polymeric coating with a more rapid and less sustained drug release results in reduced therapeutic efficacy. Interventional cardiologists are familiar with ISR in BMS, however, the restenotic process in BMS seems to be gradual, slowly over time occurring and not aggressive as in the cases described here. We hypothesise that the micro-structured stent surface could exert negative effects onto the vessel wall resulting in early and severe ISR. Our study has limitations. Most notably, the number of patients is relatively small and not all procedures were done under IVUS guidance. Although stent under-sizing can never be fully ruled out without IVUS guidance, this possibility seems unlikely to fully explain the high rate of ISR observed in our study population. Therefore, we feel that post marketing real-world data collection at a larger scale is essential to investigate this potentially serious problem.

Conflicts of interest

The authors have none to declare.

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