The Firehawk stent: a review of a novel abluminal groove-filled biodegradable polymer sirolimus-eluting stent

El *stent* Firehawk: revisión de un nuevo *stent* de polímero biodegradable liberador de sirolimus desde ranuras abluminales

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ABSTRACT

Despite recent advances in drug-eluting stent (DES) technology, late adverse events remain concerns after percutaneous coronary intervention. The persistence of polymer material on DES has been suggested as a trigger for chronic inflammation.The Firehawk, a novel DES, has a unique design with recessed abluminal grooves, to which sirolimus and biodegradable polymer are applied. The Firehawk stent is designed to minimize polymer volume and antiproliferative drug concentration to reduce inflammation and hypersensitivity reactions. Several recent trials have reported the clinical outcomes of this device. This article provides a review of the current clinical evidence concerning the Firehawk stent.

Keywords: *coronary disease, drug eluting stent, biodegradable polymer.*

RESUMEN

A pesar de los recientes avances en la tecnología con los *stents* liberadores de farmacos (DES), los eventos cardíacos adversos tardíos permanecen siendo una preocupación. La presencia de polímeros no absorbibles se ha sugerido como causa de inflamación crónica. El *stent* Firehawk presenta un diseño muy especial que combina un polímero absorbible con localización abluminal de reservorio de la droga, lo que potencialmente podría reducir la inflamación y las reacciones de hipersensibilidad.
Se han realizado varios estudios aleatorizados y observacionales con este diseño de *stent* y en este artículo se hace una revisión de los datos clínicos más relevantes con este diseño de DES

Palabras clave: *enfermedad coronaria, stent farmacológico, polímeros biodegradables.*

Revista Argentina de Cardioangiología Intervencionista 2019;10(2):73-77. https://doi.org/10.30567/RACI/201902/0073-0077

INTRODUCTION

Percutaneous coronary intervention (PCI) has revolutionized the treatment of patients with coronary artery disease, which is one of the leading cause of death worldwide[1]. While the introduction of bare metal stents improved procedural success and acute outcomes when compared to balloon angioplasty[2], the rate of in-stent restenosis remained high. Drug-eluting stents (DES) were developed to deliver antiproliferative drugs to the vessel wall, resulting in significantly reduced angiographic and clinical measures of restenosis[3]. To date, DES have been shown to have superior safety and efficacy compared to bare metal stents[4], and new-generation DES, which have incorporated thinner struts, new antiproliferative drugs with better elution profiles, and biocompatible polymers, are currently recommended for all patient and lesion subtypes in PCI[5]. Although new-generation DES include both durable and biodegradable polymer-coated stents, antiproliferative drugs and the lifelong presence of durable polymer are associated with chronic local inflammation, hypersensitivity reactions, delayed reendothelialization, impaired endothelial function, and neoatherosclerosis, leading to late adverse clinical events[6-9].

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Conflictos de intereses: Alexandra Lansky has received a research grant and speaker fee from Microport. The other authors have reported no conflict of interests.

Recibido: 31/05/2019 | Aceptado: 07/06/2019

The Firehawk stent (Shanghai MicroPort Medical Group, Shanghai, China) is a novel thin strut cobalt-chromium coronary stent with sirolimus and biodegradable polymer that are localized to a series of abluminal grooves. The design of the stent minimizes polymer burden and reduces drug concentrations, making it more biocompatible than a conventional DES. Recently, several clinical studies have reported the safety and efficacy of the Firehawk. This review summarizes the unique design and concept of this device and the clinical evidence of the Firehawk stent.

STENT DESIGN AND CONCEPT OF THE FIREHAWK

The Firehawk is a balloon-expandable L605 cobalt-chromium stent with a strut thickness of 86 μm pre-mounted on a rapid exchange delivery system. A novel feature of this device is the unique set of recessed abluminal grooves along its outer surface containing a D,L-polylactic acid polymer of 10 μm thickness, which provides for the controlled and targeted release of the antiproliferative drug sirolimus into the vessel wall (**Figure 1**). Polylactic acid polymer is biodegradable and is readily metabolized to carbon dioxide and water. Inflammation associated with the polymer subsides as it degrades and the drug is delivered. The remainder of the stent's surface (>80%) is metallic. The drug density of sirolimus is 0.3 μg/mm^2, with 90% of the dose released in the first 90 days. The polymer degrades from the stent over the course of 6 to 9 months, leaving only the metallic stent behind. The characteristics of the Firehawk stent is summarized in **Table 1.**

The Firehawk stent is designed to minimize polymer burden and reduce drug concentrations in the vessel wall. In fact, it represents the lowest polymer volume and drug concentration among currently available biodegradable polymer DES[10]. In a

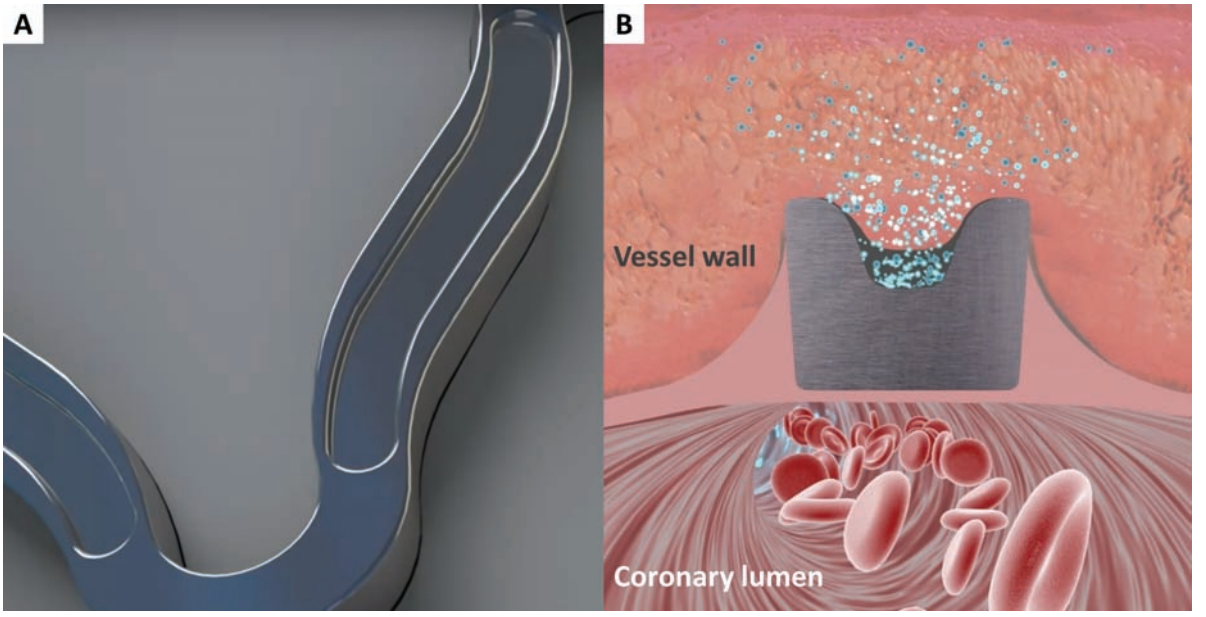

Figure 1 *Stent appearance and conceptual drug releasing in the vessel wall. (A) Recessed abluminal grooves at the outer surface. (B) Abluminal grooves contain sirolimus and biodegradable polymer to provide controlled and targeted antiproliferative effect.*

TABLE 1. The characteristics of the Firehawk stent.

Platform	
Stent material	L605 cobalt-chromium with abluminal grooves
Strut thickness	86 µm
Number of links	2 or 3
Stent diameter	2.25, 2.50, 2.75, 3.00, 3.50, 4.00 mm
Stent length	13, 16, 18, 21, 23, 26, 29, 31, 33, 35, 38 mm
Carrier	
Polymer	D,L-polylactic acid biodegradable polymer
Coating	Abluminal
Drug	
Sirolimus	0.30 µg/mm^2
Release profile	90% release by 90 days

2.25×31 mm, 2.25×33 mm, 2.25×35 mm, 2.25×38 mm, 2.5×35 mm and 2.5×38 mm are not available.

porcine model, the use of abluminal grooves allowed an equivalent concentration of sirolimus to be delivered to the endothelial tissue while decreasing the amount of circulating drug by nearly 7-fold when compared to the conventional Cypher sirolimus-eluting stent (Johnson & Johnson, New Brunswick, USA) (113 pg/ml vs. 733 pg/ml)[11]. The Firehawk stent demonstrated lower inflammation scores, and despite its abluminal groove design, was shown to have similar mechanical performance under expansion and contraction when compared to traditional DES[11]. In the context of these conceptual advantages, the Firehawk stent has been evaluated in clinical trials.

CLINICAL EVIDENCE

The first-in-man study of the Firehawk was published in 2012. There have been two subsequent randomized control trials (RCT) and one single-arm prospective registry further evaluating the device's performance **(Table 2).** The first study included only 21 patients with single *de novo* native coronary lesions at a single Chinese site[12]. Device success was achieved in all but one patient, where the stent deployed with >30% residual stenosis that was resolved after post-dilation. Target lesion failure (TLF) —a composite cardiac death, myocardial infarction (MI), and ischemia-driven target lesion revascularization—was 0% at 30 days. Follow-up angiography revealed late lumen loss (LLL) of 0.13±0.18 mm and 0.16±0.07 mm at 4 and 13 months. An optical coherence tomography (OCT) follow-up was performed in 14 patients, suggesting good vessel healing after Firehawk implantation with 96.2% of struts covered and a low rate of strut malapposition (0.1%) **(Table 3)**[12]. Although the number of enrolled patients was very limited, this first-in man study provided promising results.

The TARGET I trial was a RCT comparing the performance of the Firehawk stent to the XIENCE durable-polymer everolimus-eluting stent (Abbott Vascular, Santa Clara, USA) in non-complex patients and lesions **(Table 2)**[13]. The study enrolled 458 patients from 16 Chinese sites, with 227 randomized to the experimental group. The Firehawk had similar LLL to the XIENCE stent at 9 months (0.13±0.24 mm vs. 0.13±0.18 mm, p for non-inferiority <0.0001). Although TLF was a secondary endpoint of this study, its incidence was also equivalent between Firehawk and XIENCE stent at 12-month follow-up (2.2% vs. 2.2%, p=1.00)[13]. This result reinforced the clinical safety and efficacy of the Firehawk stent compared to the best-in-class XIENCE DES. However, the sample size of the TARGET I trial was calibrated to assess a difference in LLL, and the event rate was low because of strict angiographic and clinical eligibility criteria, limiting the statistical power of this comparison.

TARGET II was a prospective, multicenter, single-arm registry assessing the performance of the Firehawk stent in patients with higher lesion complexity than in the first-in-man study and TARGET I trial **(Table 2)**[14]. A total of 730 patients were enrolled and treated with Firehawk stents in China. In this study, multiple stent implantations into lesions up to 60 mm in length were allowed. The primary endpoint of the study was TLF at 12 months,which was low (4.4%) with only one definite or probable stent thrombosis reported. When the participants were divided into three groups according to coronary lesion complexity, patients

TABLE 2. Clinical trials to evaluate safety and/or efficacy of the Firehawk stent.

	FIM FIREHAWK[12]	TARGET I[13]	TARGET II[14]	TARGET All Comers[10]
First published year	2012	2013	2014	2018
Design	Single-arm registry	RCT	Single-arm registry	RCT
Comparator	N/A	XIENCE	N/A	XIENCE
Sample size (n)	21	458 (227 vs. 231)	730	1653 (823 vs. 830)
Region	China	China	China	Europe
Major inclusion criteria	Single denovo lesion ≤30 mm	Single denovo lesion ≤24 mm	Denovo lesion ≤60 mm	All-comers study
Major exclusion criteria	Acute MI	Age >75, acute MI, CTO, LMT, bifurcation lesion	Age >75, acute MI, LMT, 3 vessel disease, severe Ca	None
Patient characteristics				
Age (years)	56.2±8.9	58.7±9.4	58.7±8.9	64.9±9.8
Male	67%	69%	71%	78%
Hypertension	43%	58%	60%	60%
Diabetes	14%	14%	26%	24%
Hyperlipidemia	57%	27%	34%	53%
Prior MI	10%	20%	30%	22%
Acute MI	0%	0%	0%	31%
Lesion characteristics				
RVD (mm)	2.88±0.51	2.87±0.47	2.79±0.49	2.77±0.49
Lesion length (mm)	17.7±6.1	15.7±7.1	23.9±13.1	19.0±11.8
Diameter stenosis	68.4±12.6%	66.4±13.2%	71.2±15.5%	71.7±15.9%
Primary endpoint	TLF at 30 days	LLL at 9 months	TLF at 12 months	TLF at 12 months
Results	0%	0.13±0.24 mm vs. 0.13±0.18 mm	4.4%	6.1% vs. 5.9%

Only patient and lesion characteristics in the Firehawk group are listed in TARGET I trial and TARGET All Comers study. TLF was defined as a composite of cardiac death, MI, and ischemia driven target lesion revascularization. Sample size and results are shown as the Firehawk vs. XIENCE in TARGET I trial and TARGET All Comers study.
Ca, calcification; CTO, chronic total occlusion; FIM, first in man; LLL, late lumen loss; LMT, left main trunk; MI, myocardial infarction; RCT, randomized control trial; RVD, reference vessel diameter; TLF, target lesion failure.

TABLE 3. Optical coherence tomography substudies.

	FIM FIREHAWK[12]	TARGET I17			TARGET All Comers16		
	(n=14)	Firehawk (n=20)	XIENCE (n=23)	p-value	Firehawk (n=24)	XIENCE (n=28)	p-value
Time (months)	13		36			3	
Uncovered struts	3.8%	0.8%	0.7%	0.53	0.1±0.3%	0.0±0.1%	0.26
Malapposition	0.1%	0.08%	0.06%	0.15	1.0±1.6%	1.2±2.0%	0.77
Neointimal thickness (μm)	64±55	130±20	130±20	0.80	75.5±25.8	82.3±31.1	0.40

FIM, first in man.

in the top SYNTAX score tertile (>12) had a significantly higher rate of TLF compared to those in the intermediate and low tertiles (7.5% vs. 3.1% vs. 2.5%, p=0.02).[14] Thereafter, a patient-level pooled analysis of the TARGET trials was published including 2-year results. The follow-up data from 1007 patients yielded a TLF incidence of 4.6% at 24 months with only one case of stent thrombosis (0.1%).[15] These findings suggest that the safety of the Firehawk stent is in line with conventional DES. Based on the clinical evaluations in China, the Firehawk stent received a ConformitéEuropéenne mark in 2015. However, neither TARGET I nor II included patients with high-risk clinical (e.g. elderly and acute MI) and lesion (e.g. severe calcification, left main disease, and bypass lesion) profiles. Thus, an all-comers RCT which is adequately powered to assess clinical events was warranted.

The TARGET All-Comers study was a prospective, multicenter, open-label randomized non-inferiority trial again comparing the Firehawk and XIENCE stent (**Table 2**)[10]. From December 2015 to October 2016, 1653 patients from 21 medical centers in 10 European countries were enrolled and 823 were randomized to treatment with the Firehawk stent. There were no restrictions on the lesion characteristics, PCI procedures, or patient's clinical presentation. The included participants were older than previous studies and acute MI accounted for approximately 30%. The incidence of TLF was 6.1% in the Firehawk group and 5.9% in the XIENCE group (p for non-inferiority=0.004), which was numerically higher than that in the TARGET I and II (**Figure 2).** A small but significant difference in the technical success rate favored the XIENCE stent (95.6% vs. 94.2%, p=0.01), which may represent a limitation of an open-label device study, in which behavioral differences based on investigator experience cannot be excluded. The angiographic substudy of 176 patients showed that LLL was 0.17±0.48 mm and 0.11±0.52 mm for patients in the Firehawk and XIENCE groups (p for non-inferiority=0.02). In a subgroup analysis, there were no significant between-group differences with respect to prespecified clinical and lesion characteristics.[10] The TARGET All-Comers study clearly demonstrated that the Firehawk stent is non-inferior to the benchmark XIENCE stent as assessed with the primary endpoint of TLF at 12 months in an all-comers population. Furthermore, the results confirmed the clinical evaluations performed in China, and represent a successful global approval pathway for a Chinese DES in Europe. An OCT substudy of TARGET All-Comers assessed neointimal coverage at 3 months in 36 patients with 52 lesions[16]. The Firehawk and XIENCE groups both displayed near-complete strut coverage, low rate of malappo sed struts,and neointimal thicknesses of 75.5±25.8 μm and 82.3±31.1 μm (p for non-inferiority <0.001). The results of the OCT substudies performed in the first-in-man study, TARGET I trial, and TAR-

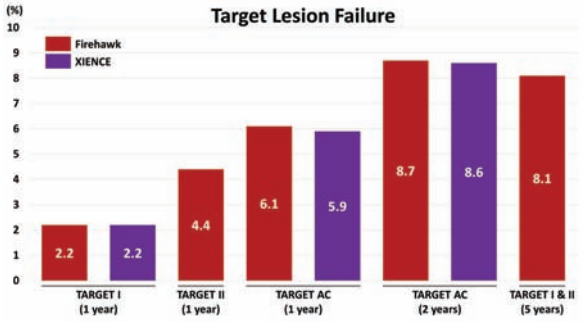

Figure 2 *The incidence of target lesion failure in clinical trials. Target lesion failure is defined as a composite of cardiac death, myocardial infarction, and ischemia-driven target lesion revascularization.*

GET All-Comers study are summarized in **Table 3,** indicating consistent vessel healing demonstrated with the Firehawk up to 3 years[12,16,17]. Compared to previous results with other biodegradable polymer DES, OCT findings with the Firehawk stent appears to be favorable[16]. Most recently, the 2-year clinical outcomes of TARGET All-Comers study was published, showing similar safety and efficacy profiles of the Firehawk and XIENCE stents[18]. It is conceivable that the Firehawk is a safe and effective alternative stent to treat patients with coronary artery disease in daily clinical practice.

The Firehawk stent has been tested in patients highly selected by angiographic and clinical characteristics in TARGET I trial, followed by TARGET II which included long lesions and TARGET All Comers study. Accordingly, event rates have been substantially increased in these studies **(Figure 2),** but the Firehawk stent has shown consistent safety and efficacy. However, whether biodegradable polymer DESs have a clinical advantage is still under debate. A pooled analysis of 3 DES RCTs reported lower rates of definite stent thrombosis and clinically indicated target lesion revascularization at 4 years with biodegradable polymer DES implantation compared to durable polymer DES, but the tested durable polymer devices were first-generation DES in this investigation[19]. On the other hand, a recent meta-analysis which included 16 randomized DES trials demonstrated similar safety and efficacy of biodegradable polymer DES in terms of TLF and stent thrombosis during a mean follow-up period of 26 months compared to new-generation durable polymer DES, failing to show a clinical benefit[20]. It is difficult to demonstrate the potential superiority of biodegradable polymer DES at mid-term follow-up (e.g. 2 years). The patient-level pooled analysis form TARGET I and II trials showed long-term results of the Firehawk stent.[21] However, the rate of TLF (8.1% at 5 years) was relatively low **(Figure 2),** and the result was only for the Firehawk stent without any comparator. The long-term follow-up data from the all-comers RCT is warranted to differentiate the clinical usefulness of the Firehawk stent with conceptual advantages (i.e. minimum volume of biodegradable polymer and antiproliferative drug), and the TARGET All-Comers study will continue to evaluate clinical outcomes up to 5 years.

CONCLUSION

The Firehawk stent has a unique design with recessed abluminal grooves facing the vessel wall, to which sirolimus and biodegradable polymer are applied. This novel DES is designed to minimize polymer volume and antiproliferative drug concentration to reduce inflammation and hypersensitivity reactions in the coronary vessel wall. Recent clinical evidence has supported the safety and efficacy of the Firehawk stent with non-inferiority to the XIENCE stent in the RCTs. Future investigation will elucidate whether the Firehawk has the potential to further improve clinical outcomes.

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