Original article

Safety and efficacy of a novel abluminal groove-filled biodegradable polymer sirolimus-eluting stent for the treatment of *de novo* coronary lesions: 12-month results from the TARGET II trial

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Background In the TARGET I randomized controlled trial, the novel abluminal groove-filled biodegradable polymer sirolimus-eluting stent FIREHAWK proved non-inferior to the everolimus-eluting stent in nine-month in-stent late loss in single *de novo* coronary lesions. This study was aimed at evaluating clinical safety and effectiveness of FIREHAWK in a moderately complex population (including patients with small vessels, long lesions and multi-vessels), and at validating the ability of the SYNTAX score (SS) to predict clinical outcomes in patients treated with this latest generation drug-eluting stent.

Methods TARGET II was a prospective, multicenter, single-arm study with primary outcome of 12-month target lesion failure (TLF), including cardiac death, target vessel myocardial infarction (TV-MI) and ischemia-driven target lesion revascularization (TLR). Stent thrombosis was defined according to the Academic Research Consortium (ARC) definition. Patients were grouped by tertiles of SS (≤6, >6 to ≤12, and >12). All patients were exclusively treated with the FIREHAWK stent and were followed up at 1, 6, and 12 months, and annually thereafter up to five years.

Results A total of 730 patients were included in this registry study. The 12-month incidence of TLF was 4.4% and the incidence of TLF components were, cardiac death 0.5%, TV-MI 3.2%, and TLR 2.2%. One definite/probable stent thrombosis was observed at 12-month follow-up. Mean SS was 10.87±6.87. Patients in the SS >12 tertile had significantly higher TLF (P=0.02) and TLR (P <0.01) rates than those in lower SS groups. In COX proportional-hazards regression analyses, TLF incidence was strongly related to lesion length (long lesion vs. non-long lesion patients; *HR* 3.416, 95% *CI*, 1.622–7.195), but unrelated to diabetic, small vessel, and multivessel subgroups.

Conclusions The low TLF incidence in this study indicates that FIREHAWK is safe and effective in the treatment of moderately complex coronary disease. SS is also able to predict adverse clinical outcomes in FIREHAWK treated patients. (Clinical Trial.gov identifier: NCT0141264)

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First-generation drug-eluting stents (DESs) reduced clinical restenosis compared with bare metal stents (BMSs);[1] however, pathological studies showed that their durable polymers were associated with chronic inflammation and delayed arterial healing, possibly underlying increased risk for very late stent thrombosis (ST) as compared with BMS.[2] Second-generation DES were then developed, and although available data suggest superiority relative to first-generation DES in terms of preventing restenosis without significant untoward events,[3] increased risk of late and very late ST remained a concern.[4,5] Because both drug and durable polymer by causing delayed endothelial healing are considered significant factors for ST,[6] a third-generation DES was developed, the FIREHAWK biodegradable-polymer sirolimus-eluting stent system. Sirolimus and PLA polymer complex are poured into abluminal grooves in the outer surface of the cobalt-chromium alloy-based FIREHAWK stent which allows targeted drug release to the blood vessel wall.

The TARGET I trial demonstrated the safety and effectiveness of the FIREHAWK abluminal-groove-filled biodegradable-polymer sirolimus-eluting stent system compared to XIENCE V in 458 patients with low complexity anatomic characteristics.[7] However, in

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"real-world" practice, many patients have more complex anatomic characteristics (lesions in small vessels, long lesions, and multi-vessel disease) associated with worse clinical outcomes after percutaneous coronary intervention (PCI).[8-10] This study, TARGET II, therefore evaluated safety and efficacy of the FIREHAWK stent in a large and more complex population.

The SYNTAX score (SS), based on the location and characteristics of lesions within the coronary vasculature, is an angiographic tool to grade coronary lesion complexity.[11] SS has demonstrated value in treatment selection and prediction of clinical outcomes after PCI,[12,13] primarily in studies of first-generation DES. The prognostic value of SS in patients treated with the latest generation DES has not been investigated; we therefore also aimed at validating the predictive capacity of the SYNTAX score in patients treated with the FIREHAWK stent.

METHODS

Study design and patient population

TARGET II, a prospective, multicenter, single-arm clinical trial, enrolled a total of 730 patients who underwent PCI of *de novo* lesions in native coronary arteries in 24 cardiac centers in China from August 2011 to February 2012. The main inclusion criteria were: age between 18–75 years; stable/unstable angina, old myocardial infarction (OMI), or documented ischemia; target lesions with a diameter of the stenosis ≥70%, reference vessel diameter 2.5 mm to 4.0 mm and lesion length ≤60 mm by visual estimate; and designation to be implanted with the FIREHAWK stent only. Exclusion criteria were: acute myocardial infarction (AMI) within 72 hours; unprotected left main coronary artery or three-vessel disease requiring treatment; severely calcified lesion impeding pre-dilatation; extreme tortuosity proximal to the lesion precluding adequate stent delivery; NYHA >III or left ventricular ejection fraction (LVEF) <40%; and prior stenting within one year. All patients were to be followed up at 1, 6, and 12 months, and thereafter annually up to five years. Before PCI, all patients received treatment with aspirin (300 mg, at least 24 hours before the intervention) and clopidogrel (loading dose of 300 mg at least six hours before the intervention; no loading needed if patient was already on 75 mg/d clopidogrel for more than 72 hours). During the procedure an anticoagulant (e.g., heparin) was administered according to protocol recommendations. Dual antiplatelet therapy (DAPT) with aspirin (100–300 mg/d) and clopidogrel (75 mg/d) was continued for at least 12 months after the index procedure.

Study device

The FIREHAWK stent (MicroPort Medical, Shanghai, China) is pre-mounted on a rapid-exchange delivery system, and has three components: a cobalt-chromium L605 platform, PLA polymer, and the antiproliferative drug sirolimus. Design feature details have been previously described.[7,14]

Study endpoints and definitions

The primary endpoint of the study was target lesion failure (TLF) defined as the (device-oriented) composite of cardiac death, target vessel myocardial infarction (MI), or ischemia-driven target lesion revascularization (TLR) at 12 months follow-up. Secondary procedure-related endpoints were: (1) device, lesion, and clinical success rates (device success was defined as attainment of <50% residual stenosis of the target lesion using only the assigned device; lesion success as attainment of <50% residual stenosis, thrombolysis in myocardial infarction (TIMI) 3 flow, no residual dissection and thrombosis of the target lesion using any percutaneous method; and clinical success as attainment of lesion success of the target lesion and no in-hospital major adverse cardiac event); (2) TLF at 1, 6, and 12 months, and annually up to five years; (3) patient-oriented composite of events including all-cause death, all MI, or any revascularization reported at 1, 6, and 12 months, and annually up to five years; and (4) definite and probable stent thrombosis per Academic Research Consortium (ARC) definition criteria.[15] MI classification and diagnostic criteria were according to the third universal definition of MI.[16]

Quantitative coronary angiography and clinical events committee Quantitative coronary angiography (QCA) was performed at baseline and assessed by an independent core laboratory (CCRF, Beijing, China). An independent clinical events committee (CEC) evaluated the consistency of event adjudication on the basis of interpretation of study-specific event guidelines.

SYNTAX score assessment

SS was assessed visually by three experienced imaging analysts from an independent core laboratory (CCRF, Beijing, China). Each lesion with >50% diameter stenosis in vessels ≤1.5 mm in diameter was scored using the SS algorithm described previously.[11] Patients were categorized into low (≤6), mid (>6 to ≤12) and high (>12) baseline SYNTAX score groups.

Statistical analysis

The China Food and Drug Administration (CFDA) required more than 721 FIREHAWK treated patients for this registry study in addition to 279 patients in TARGET I trial who have received FIREHAWK treatment.[7,17] All data were analyzed according to the intention-to-treat (ITT) principle. Categorical variables are described by counts and percentages, and continuous variables are expressed as mean±standard deviation (SD). Descriptive analysis was used to assess baseline demographic variables. For the primary efficacy endpoint of TLF at 12 months the incidence and exact 95% confidence intervals were calculated. Descriptive statistics were also used to evaluate the effectiveness endpoints. Furthermore, the performance, extent and relations to the stent of all adverse events were described for safety assessment. The Cox proportional hazards model was used to analyze the relevance between clinical outcomes and baseline demographics,

index procedure-related parameters and other indicators. Subgroup analysis of outcome was conducted based on: lesion length (defined as patients with at least one target lesion with a lesion length ≥30 mm by QCA); reference vessel diameter (RVD) (small vessel group defined as patients with at least one target lesion with a RVD ≤2.5 mm by QCA); number of vessels with lesions (more than one vessel with stenosis >50%); and diabetes status. All statistical tests were two-sided with a 0.05 level of significance. All analyses were performed with the SAS 9.13 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient, lesion and procedural characteristics

A total of 730 patients (with 1 008 target lesions) were enrolled at 24 sites to receive FIREHAWK stent treatment. Baseline and clinical characteristics are shown in Table 1. The mean age was 58.7±8.9 years old, 25.9% of enrolled patients had diabetes mellitus, and mean LVEF was 61.8±8.2. A total of 1 256 stents were implanted. SYNTAX score varied from 1 to 43 with a mean score of 10.87±6.87 in 729 patients (one patient lacked SS secondary to technique). Device and lesion success rate was very high, 99.7% and 98.9%, respectively (Table 2).

Clinical outcomes at 12-month follow-up

The observed composite primary endpoint of TLF was 4.4%. Only one patient experienced definite stent thrombosis. Table 3 summarizes 12-month clinical outcomes.

Clinical outcomes among patients in different SS tertiles

Patients were stratified into low-, mid- and high-tertile groups based on baseline SS, ≤6, >6 to ≤12, and >12, respectively. Patients in SYNTAX score in the >12 tertile had significantly higher TLF (P=0.02), patient-oriented composite endpoints (P <0.01, composite of all-cause death, all MI and any revascularization), and revascularization rates (P <0.01) than those in lower SS groups at one year (Table 4).

Table 1. Baseline demographics FIREHAWK patient (n=730)

Variables	Values
Age (years)	58.7±8.9
Male gender	517 (70.8)
Hypertension	439 (60.1)
Hypercholesterolemia	249 (34.1)
Diabetes mellitus	189 (25.9)
Insulin-treated diabetes mellitus	61 (32.3)
Current smoker	272 (37.3)
Family history of CAD	55 (7.5)
Peripheral vessel disease	59 (8.1)
Prior PCI	58 (7.9)
Prior CABG	6 (0.8)
Prior MI	221 (30.3)
Angina	
Stable angina	155 (21.2)
Unstable angina	505 (69.2)
Silent ischemia	18 (2.5)
LVEF (%)	61.8±8.2

Values are expressed as n (%) or mean±SD. CAD: coronary artery disease; MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; LVEF: left ventricular ejection fraction.

Table 2. Lesion characteristics and procedural results (FIREHAWK patient, n=730; lesion, n=1 008; stent, n=1 258)

Variables	Values
Target lesion assessment	
Target lesions per patient	1.38±0.61
Lesion location	
LAD	524 (52.0)
LCX	200 (19.8)
RCA	284 (28.2)
TIMI flow pre-procedure (N_{lesion}=988)	
0	74 (7.5)
I	29 (2.9)
II	89 (9.0)
III	796 (80.6)
Baseline QCA	
Reference vessel diameter (mm)	2.79±0.49
Lesion length (mm)	23.9±13.1
Minimal lumen diameter (mm)	0.82±0.47
Diameter stenosis (%)	71.2±15.5
SYNTAX score	10.87±6.87
Procedural results	
Predilation	803 (79.7)
Access sites	
Transradial approach	664 (91.0)
Transfemoral approach	62 (8.5)
Transradial+femoral approach	4 (0.5)
Stents per lesion	1.27±0.52
Stent diameter (mm)	3.06±0.45
Postdilation	459 (45.5)
Post-procedural QCA	
Reference vessel diameter (mm)	2.91±0.48
Minimal lumen diameter (mm)	
In-stent	2.62±0.45
In-segment	2.34±0.52
Diameter stenosis (%)	
In-stent	9.7±5.3
In-segment	16.2±10.0
Acute gain (mm)	
In-stent	1.81±0.52
In-segment	1.53±0.55
Success rates	
Device success	1 254 (99.7)
Lesion success	987 (98.9)

Values are expressed as n (%) or mean±SD. QCA: quantitative coronary angiography, LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery.

Table 3. Clinical outcomes (n=730)

Variables	30 days	12 months
Death	2 (0.3)	7 (1.0)
Cardiac death	1 (0.1)	4 (0.5)
Non-cardiac death	1 (0.1)	3 (0.1)
Myocardial infarction	21 (2.9)	23 (3.2)
Q wave MI	1 (0.1)	1 (0.1)
Non-Q wave MI	20 (2.7)	22 (3.1)
TV-MI	21 (2.9)	23 (3.2)
Any revascularization	3 (0.4)	22 (3.0)
TLR	1 (0.1)	8 (2.2)
TVR	2 (0.3)	9 (1.2)
TLF	22 (3.0)	32 (4.4)
PoCE	24 (3.3)	46 (6.3)
Definite/probable stent thrombosis	1 (0.1)	1 (0.1)

Values are expressed as n (%). MI: myocardial infarction; TV-MI: target vessel myocardial infarction; TLR: ischemia-driven target lesion revascularization; TVR: target vessel revascularization; TLF: target lesion failure (a composite of cardiac death, TV-MI and TLR); PoCE: patient-oriented composite endpoint (a composite of all death, all MI and any revascularization).

Table 4. Clinical outcomes according to SYNTAX score tertiles at 12 months

Variables	SS ≤6 (*n*=197)	6 <SS ≤12 (*n*=291)	SS >12 (*n*=241)	*P* values
Death	1 (0.5)	3 (1)	3 (1.2)	0.70
Cardiac death	0 (0)	2 (0.7)	2 (0.8)	0.28
MI	4 (2.0)	7 (2.4)	12 (5.0)	0.15
Any revascularization	3 (1.5)	4 (1.4)	15 (6.2)	<0.01
TLR	1 (0.5)	0 (0)	7 (2.9)	<0.01
TVR	1 (0.5)	0 (0)	8 (3.3)	<0.01
TLF	5 (2.5)	9 (3.1)	18 (7.5)	0.02
PoCE	8 (4.1)	13 (4.5)	25 (10.4)	<0.01

Values are expressed as *n* (%). SS: SYNTAX score; MI: myocardial infarction; TLR: ischemia-driven target lesion revascularization; TVR: target vessel revascularization; TLF: target lesion failure (a composite of cardiac death, TV-MI and TLR); PoCE: patient-oriented composite endpoint (a composite of all death, all MI and any revascularization).

Subgroup analysis

Both clinical incidence and COX proportional-hazards regression analysis showed that the TLF incidence was strongly related to lesion length (long lesion vs. non-long lesion patients; *HR* 3.416, 95% *CI*, 1.622–7.195) but unrelated to diabetic status (diabetic patients vs. non-diabetic patients; *HR* 1.713, 95% *CI*, 0.828–3.546), vessel diameter (small vessel disease vs. non-small vessel disease; *HR* 1.010, 95% *CI* 0.476–2.146), and number of diseased vessels (multivessel disease vs. non-multivessel disease; *HR* 1.101, 95% *CI* 0.509–2.380) (Figure 1).

DISCUSSION

The safety of the FIREHAWK stent has been confirmed in populations of patients with low complexity lesions in the FIREHAWK FIM and TARGET I trials (RCT & Long Cohort).[7,14,17] The objective of the TARGET II registry study was to evaluate the safety and efficacy of the FIREHAWK stent in patients with more complex lesion types.

Clinical safety and efficacy

The composite primary endpoint TLF was low at 30 days (3.0%) and remained low at 12 months (4.4%). All-cause death, cardiac death, TV-MI and TLR at 12-month follow-up was 1.0%, 0.5%, 3.2%, and 1.1%, respectively, with only one definite/probable stent thrombosis. These results are similar or lower than those with other DES used worldwide. For example, in SPIRIT IV the one-year TLF rate of XIENCE V was 4.2% and 5.1% in restrictively selected[18] and in "real-world" patients.[19] The incidence of ST in this study is significantly lower than that for XIENCE V (0.1% vs. 0.3%) which has been demonstrated to be associated with reduced ST.[18] These results indicate that the FIREHAWK stent is safe and effective in a moderately complex patient population.

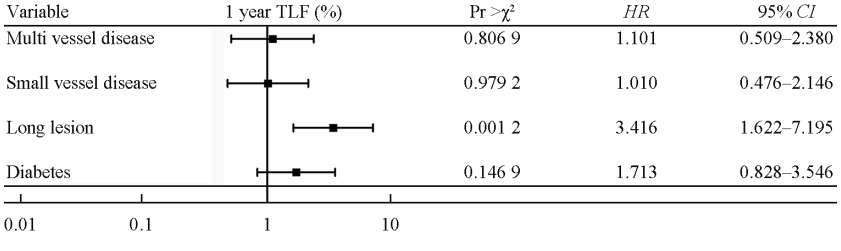

Figure 1. Results of COX proportional-Hazards regression. TLF: target lesion failure (including cardiac death, target vessel myocardial infarction and ischemic-driven target lesion revascularization).

The clinical benefits of DES mainly relate to stent design, drug and polymer. The FIREHAWK stent has the unique design feature of localizing to abluminal grooves in its struts the biodegradable polymer which fully metabolizes to water and carbon dioxide within six to nine months. Meanwhile, this unique groove-filled biodegradable polymer design has minimal contact with the intima, a design that might be associated with decreased polymer-related inflammation. By releasing drug directly into the arterial wall, this design allows use of less drug; the average sirolimus dosage in the FIREHAWK is only 3 μg/mm stent length which is 1/3 of that in the XIENCE V. Therefore, it appears that the FIREHAWK stent has reasonably low rates of adverse events. However, long-term follow-up is still needed to confirm these clinical results, and all patients in this study will be followed up annually for up to five years.

Subgroup analysis

Subgroup analysis showed that the incidence of TLF at one year in the diabetic, small vessel, and multivessel subgroups did not significantly differ from that observed in their lesser complex counterparts, except for TLF being higher in patients with long lesions and having high SYNTAX scores. Diabetic status, small vessel size, and target vessel number have all been reported as risk factors for adverse outcomes such as restenosis, repeat revascularization, stent thrombosis, MI, and death.[20-24] Interestingly, in this study, it showed that factors did not significantly increase clinical adverse events (Figure 1). These results indicate that the FIREHAWK stent shows outstanding performance in patients with diabetes, small vessel disease and multivessel disease as compared to patients without said conditions, and therefore could be considered safe and effective in treating patients with these characteristics.

Cox regression showed that long lesion was an independent predictor for TLF (*HR* 3.416, 95% *CI* 1.622–7.195) which is in agreement with other studies.[8] Although the TLF rate was higher in patients with long lesions than in those with non-long lesions (8.2% vs. 2.5%, *P* <0.001), it is still much lower compared with other long stent studies. For example, in the LONG-DES-III study, the TLF of the EES and SES groups were 12.9% and 9.7%, respectively.[25] On the other hand, the incidence of TLF in the long stent group was mainly driven by higher periprocedural non Q-wave TV-MI which was related with the PCI process and side branch status after PCI. Although the third universal definition of MI was used in this study because it is more sensitive to detect MI than the ARC definition, the TV-MI rate of 7.0% in the long

stent subgroup in the TARGET II study was still lower than that in other studies, 9.8%, 8.0% and 9.7%.[8,25] Moreover, the long FIREHAWK stent has been previously studied in TARGET I long stent cohort.[17] Among the 50 patients with a mean lesion length of 35.16±9.44 mm who underwent FIREHAWK implantation there were no deaths, TLR, target vessel revascularization (TVR), or ST at one year after PCI, and only two patients experienced periprocedural non Q-wave TV-MI. The results for long stents in this study are consistent with those of the TARGET I long stent study, and demonstrate safety and efficacy of the FIREHAWK stent in the treatment of long coronary lesions. Further large scale randomized studies are warranted to confirm this finding.

Validation of the predictive capability of SYNTAX score in FIREHAWK treated patients

The SS is an angiographic tool to grade coronary lesion complexity[11] that has demonstrated value in predicting clinical outcomes after PCI.[12,13] SS may be useful to guide clinicians when deciding on the most appropriate revascularization modality, as has been recently endorsed in both American and European coronary revascularization guidelines (class IIa recommendation).[26] However, investigations on SS were conducted in patients treated with first-generation DES, and it is important to investigate the predictive capability of SS in biodegradable DES treated patients. Patients recruited in TARGET II had lesions with moderate complexity characteristics. Although the overall TLF incidence was very low (4.4%), patients were risk stratified based on SS cutoffs of 6 and 12. Patients with SS >12 had significantly higher rates of TLF and of the patient-oriented composite endpoint than those in lower SS groups; this was mainly driven by more repeat revascularization (Table 4). Despite there being no significant difference in rates of all-cause death, cardiac death, and MI among patients in different SS tertiles, there were numerical increases in the rates of these parameters with increasing SS. These results indicate that the SS allows prediction of the clinical outcomes, especially in patients treated with biodegradable DES FIREHAWK stent requiring repeat revascularization. These findings could benefit from further daily clinical practice and research on biodegradable DES.

Study limitations

This study was limited by the single arm design and inherent lack of a control arm for direct comparison. In addition, despite the non-randomized nature of the study, inclusion/exclusion criteria in the protocol were strict.

Conclusions

The low incidence of TLF in the TARGET II study indicates that the FIREHAWK stent is safe and effective in the treatment of patients with moderately complex coronary disease, and it is a promising treatment option for those patients. SS has the potential to predict adverse clinical outcomes in patients treated with the FIREHAWK stent.

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