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2-Year Clinical Outcomes of an Abluminal Groove–Filled Biodegradable-Polymer Sirolimus-Eluting Stent Compared With a Durable-Polymer Everolimus-Eluting Stent

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ABSTRACT

OBJECTIVES The aim of this study was to assess the 2-year clinical outcomes of the Firehawk stent, a novel abluminal groove-filled biodegradable-polymer sirolimus-eluting coronary stent, compared with XIENCE, a durable-polymer everolimus-eluting coronary stent.

BACKGROUND The long-term outcomes of the Firehawk stent have not been evaluated beyond 1 year in a randomized all-comers clinical trial.

METHODS The TARGET All Comers study is a prospective, multicenter, all-comers, randomized, noninferiority trial conducted in Europe. A total of 1,653 patients were randomly assigned to undergo implantation of either the Firehawk or the XIENCE stent. The primary endpoint was target lesion failure, a composite of cardiac death, target vessel myocardial infarction, or ischemia-driven target lesion revascularization.

RESULTS At 2-year follow-up, the incidence of target lesion failure was 8.7% in the Firehawk group versus 8.6% in the XIENCE group ($p = 0.92$). The event rates of individual components of the primary endpoint were comparable for the 2 groups. Landmark analyses between 1- and 2-year follow-up revealed no statistically significant difference of TLF for the Firehawk versus the XIENCE stent. Beyond 1 year, very late definite or probable stent thrombosis occurred in 3 patients (0.4%) in the Firehawk group and in 7 patients (0.9%) in the XIENCE group ($p = 0.34$).

CONCLUSIONS The 2-year follow-up of the TARGET All Comers study confirms comparable safety and efficacy profiles of the Firehawk and XIENCE stents. (J Am Coll Cardiol Intv 2019;■:■–■) © 2019 Published by Elsevier on behalf of the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

DES = drug-eluting stent(s)

HR = hazard ratio

MI = myocardial infarction

PCI = percutaneous coronary intervention

RCT = randomized controlled trial

TLF = target lesion failure

TLR = target lesion revascularization

Drug-eluting stents (DES) have been shown to have superior safety and efficacy compared with bare-metal stents (1), and new-generation DES are currently recommended for all patient and lesion subsets in percutaneous coronary intervention (PCI) (2). Although new-generation DES include both durable and biodegradable polymer-coated stents, the lifelong presence of durable polymer, even among new-generation DES, has been associated with chronic inflammation, hypersensitivity reactions, delayed arterial healing, and neoatherosclerosis, which have been implicated in late adverse clinical events (3-5). Biodegradable-polymer DES have been designed to address this potential limitation of durable polymer. In addition to the type of stent polymer, various factors such as the type and pharmacokinetic release profile of the antiproliferative drug, reproducibility of drug elution, polymer and drug density, and thickness of stent strut affect the performance of DES (6). The Firehawk stent (Shanghai MicroPort Medical Group, Shanghai, China), a thin-strut cobalt-chromium stent that contains sirolimus with biodegradable polymer applied to recessed abluminal grooves, is designed to minimize polymer burden and reduce drug concentrations in the vessel wall. The safety and efficacy of the Firehawk have been demonstrated in low-risk patients (7,8). Although the Firehawk stent received a Conformité Européenne mark in 2015 on the basis of these study results, a post-market study including high-risk patients in a real-world clinical setting was warranted. The TARGET All Comers study recently reported noninferiority of target lesion failure (TLF) at 12 months with the Firehawk stent compared with the XIENCE durable-polymer, everolimus-eluting stent (Abbott Vascular, Santa Clara, California) (9). However, longer term results of the Firehawk stent are lacking. In the present study, we report the 2-year clinical outcomes of the TARGET All Comers study.

METHODS

STUDY DESIGN AND PARTICIPANTS. TARGET All Comers is a prospective, multicenter, open-label, randomized, noninferiority trial conducted at 21 sites in 10 European countries (NCT02520180). The ethics committee of each participating site approved the protocol, and all participants provided written informed consent. Detailed trial design and 12-month outcomes have been reported previously (9). In brief, patients with symptomatic or asymptomatic coronary artery disease and objective evidence of myocardial ischemia who were indicated for PCI were eligible if they had at least 1 epicardial coronary artery target lesion with percentage diameter stenosis of at least 50% in vessel sizes of 2.25 to 4.0 mm by visual estimation. All coronary syndromes, de novo and restenotic lesions, chronic total occlusions, and native coronary or bypass lesions were permitted. There was no limit on the total number of treated lesions or vessels, lesion length, or number of stents. The broad inclusion criteria were intended to reflect routine clinical practice. Major exclusion criteria were intolerance to aspirin, $P2Y_{12}$ inhibitor, heparin, DES components, or contrast material and planned surgery within 6 months at the time of index PCI. Patients who met the entry criteria were randomly allocated in a 1:1 ratio and an open-label manner to treatment with the Firehawk or the XIENCE stent using a web-based system, stratified by clinical site and ST-segment elevation myocardial infarction (MI). Optical coherence tomography at 3 months and angiographic substudies have been reported previously (9,10). The clinical event committee and core laboratories were masked to the allocated

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DES, whereas treating physicians and patients were not.

STUDY DEVICES AND PROCEDURES. The Firehawk stent is a balloon-expandable L605 cobalt-chromium stent platform with a strut thickness of 86 μm. The stent is pre-mounted on a rapid-exchange delivery system. Recessed abluminal grooves at the outer surface contain a D,L-polylactic acid biodegradable polymer of 10 μm thickness, which provides controlled release of the antiproliferative drug sirolimus. The sirolimus drug density is 0.3 μg/mm^2, with 90% release by 90 days. The polymer biodegrades within 6 to 9 months, leaving only the metallic stent (7,9,11). The control XIENCE stent is a laser-cut cobalt-chromium stent of 81 μm strut thickness coated with a 7.7-μm durable fluoride-hexafluoropropylene polymer. The everolimus drug density is 1 μg/mm^2, with virtually 100% released by 120 days.

PCI procedures were performed according to the manufacturer instructions for use provided with the assigned device and local standard practice. The same DES platform was used for all treated lesions for each patient on the basis of his or her randomized assignment. Patients were pre-treated with aspirin and a $P2Y_{12}$ inhibitor (clopidogrel, ticagrelor, or prasugrel) and continued on guideline-recommended dual-antiplatelet therapy for at least 6 months in patients in stable condition and 12 months in those presenting with acute coronary syndromes (12). Procedural anticoagulation was administered according to local standards of practice. Cardiac biomarkers (creatine kinase, creatine kinase myocardial band, and troponin I or T) were measured within 24 h before PCI and within 8 h after PCI. Clinical follow-up was scheduled at 1, 6, and 12 months and annually thereafter to 5 years.

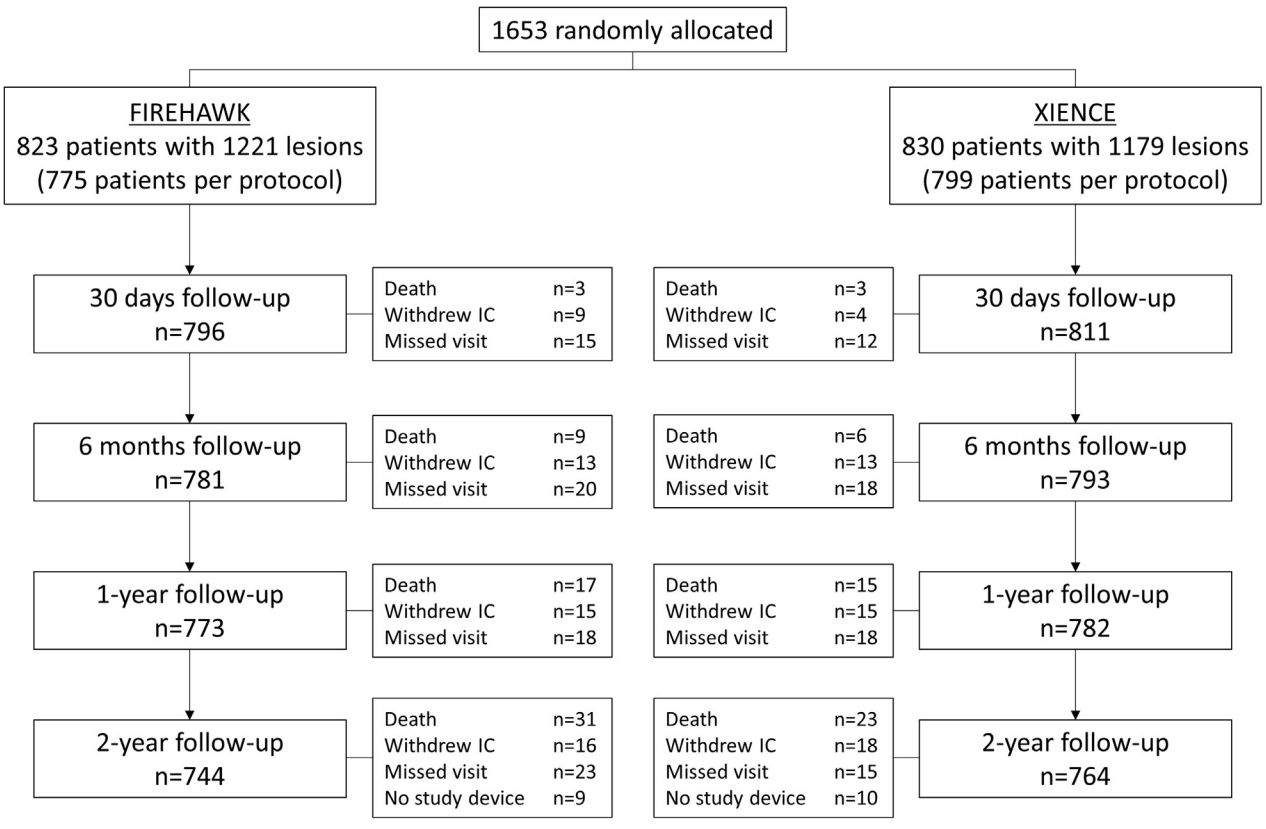
STUDY ENDPOINTS AND DEFINITIONS. The primary endpoint of the trial was TLF, a composite of cardiac death, target vessel MI, and ischemia-driven target lesion revascularization (TLR), at 12 months. Secondary endpoints included all-cause death, cardiac death, any revascularization, ischemia-driven TLR, target vessel revascularization, ischemia-driven target vessel revascularization and stent thrombosis rates as defined by the Academic Research Consortium (13), periprocedural MI as defined by the extended World Health Organization definition (14), and spontaneous MI as defined by the third universal definition (15). The patient-oriented composite endpoint was defined as a composite of all-cause death, any MI, and any revascularization. The main endpoints of interest in the present analysis are 2-year clinical outcomes including TLF and its components, definite or probable stent thrombosis, and the patient-oriented composite endpoint, as well as the pre-specified landmark analyses between 1 and 2 years. Data monitoring, management, and independent clinical event adjudication were performed by an independent clinical research organization; statistical analysis was performed by Cardialysis (Rotterdam, the Netherlands). An independent angiographic core laboratory (China Cardiovascular Research Foundation, Beijing, China) analyzed all baseline and procedural angiograms.

STATISTICAL ANALYSIS. The study was powered for noninferiority of the Firehawk compared with the XIENCE stent with respect to the primary endpoint, TLF, at 12 months. With a noninferiority margin of 3.5% and a 5% attrition rate at 12 months, enrollment of 1,656 patients provided 85% power to detect noninferiority at a 1-sided type I error level of 0.05 (9). Categorical variables are reported as counts and percentages. Categorical variables with more than 2 categories were assessed using the Mantel-Haenszel rank score test, and dichotomous variables were assessed using the Fisher exact test. Continuous variables are expressed as mean ± SD or median (interquartile range) and were compared using the Student *t* test. Time-to-event outcomes were assessed according to Kaplan-Meier methods, and the log-rank test was applied for between-group comparisons. Hazard ratios (HRs) with 95% confidential intervals were assessed using Cox proportional hazards regression analysis. We performed landmark analyses of the primary endpoint and its components by using the 1-year landmark. In addition, a chi-square test was used to assess improvement in model fit of the interaction between time (0 to 1 year and 1 to 2 years) and treatment effect (experimental vs. control) by allowing two HRs (HR for 0 to 1 year and HR for 1 to 2 years) instead of one. The intention-to-treat principle was used in the present analysis, and per protocol analysis is separately shown in Online Table 1. Pre-specified subgroup analysis was performed for the primary endpoint. A 2-sided p value <0.05 was considered to indicate statistical significance. All statistical analyses were carried out with SAS software version 9.3 (SAS Institute, Cary, North Carolina).

RESULTS

From December 17, 2015, to October 14, 2016, 1,653 patients with a total of 2,400 lesions were randomized to either Firehawk (823 patients with 1,221 lesions) or XIENCE (830 patients with 1,179 lesions), of

FIGURE 1 Study Patient Flow



Patients with no study devices implanted were followed to 1 year only. IC = informed consent.

whom 1,562 patients (94.5%) completed 2-year follow-up or had died. Thirty-eight patients (2.3%) were lost to follow-up, 34 (2.1%) withdrew their consent, and 19 (1.1%) with no study devices implanted were followed for 1 year only (**Figure 1**). The overall follow-up duration was 746 days (734 to 770 days) in the FIREHAWAK group and 745 days (735 to 767 days) in the XIENCE group.

Table 1 lists the baseline patient and lesion characteristics, which were matched between the 2 groups as shown previously (9). Overall, 728 of 1,650 patients (44.1%) presented with acute coronary syndromes, and 82.8% of treated lesions were classified by angiographic core laboratory as American College of Cardiology/American Heart Association type B2 or C (16). The 2-year clinical outcome data are presented in **Table 2**. Kaplan-Meier analysis demonstrated that the primary endpoint, TLF, occurred in 68 of 778 patients (8.7%) in the Firehawk group and 68 of 791 patients (8.6%) in the XIENCE group during 2-year follow-up ($p = 0.91$) (**Central Illustration**). The event rates of individual components of the primary endpoint and each secondary endpoint were also comparable for the 2 treatment arms (**Table 2**, Online Table 1, and **Figure 2**). Landmark analyses between 1- and 2-year follow-up showed no statistically significant differences for the Firehawk versus the XIENCE stent (Online Figure 1). A test of improvement in model fit showed no significant interactions between time and treatment effect. Beyond 1 year, very late definite or probable stent thrombosis occurred in 3 (0.4%) and 7 (0.9%) patients allocated to the Firehawk and XIENCE, respectively ($p = 0.34$). There was no device treatment interaction in TLF for any of the prespecified subgroups at 2 years (Online Figure 2).

DISCUSSION

The TARGET All Comers trial confirms that at 2 years, the abluminal groove-filled biodegradable-polymer sirolimus-eluting stent is as safe and effective as the best-in-class durable-polymer DES.

TABLE 1 Patient and Lesion Characteristics

	Firehawk (n = 823)	XIENCE (n = 830)
Age (yrs)	64.9 ± 9.8	69.2 ± 10.9
Men	641/821 (78.1)	634/830 (76.4)
Smoking (current or previous)	488/820 (59.5)	533/830 (64.2)
Diabetes mellitus	197/821 (24.0)	191/830 (23.0)
Hypertension	492/821 (59.9)	519/830 (62.5)
Hypercholesterolemia	435/821 (53.0)	425/830 (51.2)
Previous MI	178/821 (21.7)	206/830 (24.8)
Previous PCI	236/821 (28.7)	262/830 (31.6)
Previous CABG	69/821 (8.4)	62/830 (7.5)
Clinical presentation		
Stable CAD	460/820 (56.1)	462/830 (55.7)
Unstable angina	105/820 (12.8)	130/830 (15.7)
NSTEMI	186/820 (22.7)	164/830 (19.8)
STEMI	69/820 (8.4)	74/830 (8.9)
Lesions treated	1221	1179
Lesions per patient	1.5 ± 0.8	1.4 ± 0.7
Stents per patient	1.7 ± 1.0	1.7 ± 1.0
Any chronic total occlusion	47/789 (6.0)	51/792 (6.4)
Any in-stent restenosis	43/766 (5.6)	57/777 (7.3)
Stent length per lesion (mm)	26.7 ± 15.3	27.1 ± 16.9
Stent diameter (mm)	3.07 ± 0.47	3.07 ± 0.50
Lesions with core laboratory analysis	1,074	1,058
Target vessel location		
Left anterior descending coronary artery	453 (42.2)	463 (43.8)
Left circumflex coronary artery	272 (25.3)	269 (25.4)
Right coronary artery	313 (29.1)	288 (27.2)
Left main coronary artery	19 (1.8)	18 (1.7)
Bypass graft	17 (1.6)	20 (1.9)
Baseline QCA analysis		
Reference diameter (mm)	2.77 ± 0.49	2.77 ± 0.52
MLD (mm)	0.78 ± 0.47	0.79 ± 0.48
Diameter stenosis (%)	71.7 ± 15.9	71.5 ± 16.1
Lesion length (mm)	19.0 ± 11.8	18.8 ± 12.4
Final QCA analysis		
In-stent MLD (mm)	2.56 ± 0.45	2.55 ± 0.47
In-stent diameter stenosis (%)	7.4 ± 6.9	7.6 ± 6.5

Values are mean ± SD or n/N (%).

CABG = coronary artery bypass grafting; CAD = coronary artery disease; MI = myocardial infarction; MLD = minimal luminal diameter; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; QCA = quantitative coronary arteriographic; STEMI = ST-segment elevation myocardial infarction.

TABLE 2 Clinical Outcomes at 2-Year Follow-Up

	Firehawk (n = 823)	XIENCE (n = 830)	Risk Difference (95% CI)	p Value
Target lesion failure	68/778 (8.7)	68/791 (8.6)	0.1% (−2.6% to 2.9%)	0.92
Cardiac death	13/778 (1.7)	9/791 (1.1)	0.5% (−0.6% to 1.7%)	0.37
Target vessel MI	44/778 (5.7)	47/791 (5.9)	−0.3% (−2.6% to 2.0%)	0.81
Ischemia-driven TLR	20/778 (2.6)	29/791 (3.7)	−1.1% (−2.8% to 0.6%)	0.21
Target vessel failure	77/778 (9.9)	76/791 (9.6)	0.3% (−2.6% to 3.2%)	0.85
PoCE	150/778 (19.3)	141/791 (17.8)	1.5% (−2.4% to 5.3%)	0.46
All-cause death	34/778 (4.4)	25/791 (3.2)	1.2% (−0.7% to 3.1%)	0.21
Noncardiac death	21/778 (2.7)	16/791 (2.0)	0.7% (−0.8% to 2.2%)	0.38
Any MI	57/778 (7.3)	61/791 (7.7)	−0.4% (−3.0% to 2.2%)	0.77
Non-target vessel MI	14/778 (1.8)	18/791 (2.3)	−0.5% (−1.9% to 0.9%)	0.50
Any revascularization	91/778 (11.7)	93/791 (11.8)	−0.1% (−3.2% to 3.1%)	0.97
Any TVR	50/778 (6.4)	52/791 (6.6)	−0.1% (−2.6% to 2.3%)	0.91
Ischemia-driven TVR	35/778 (4.5)	41/791 (5.2)	−0.7% (−2.8% to 1.4%)	0.53
Any TLR	31/778 (4.0)	35/791 (4.4)	−0.4% (−2.4% to 1.5%)	0.66
Definite ST	12/778 (1.5)	16/791 (2.0)	−0.5% (−1.8% to 0.8%)	0.47
Definite or probable ST	13/778 (1.7)	17/791 (2.1)	−0.5% (−1.8% to 0.9%)	0.49

Values are n/N (%). Target vessel failure was defined as a composite of cardiac death, target vessel MI, and ischemia-driven TVR.

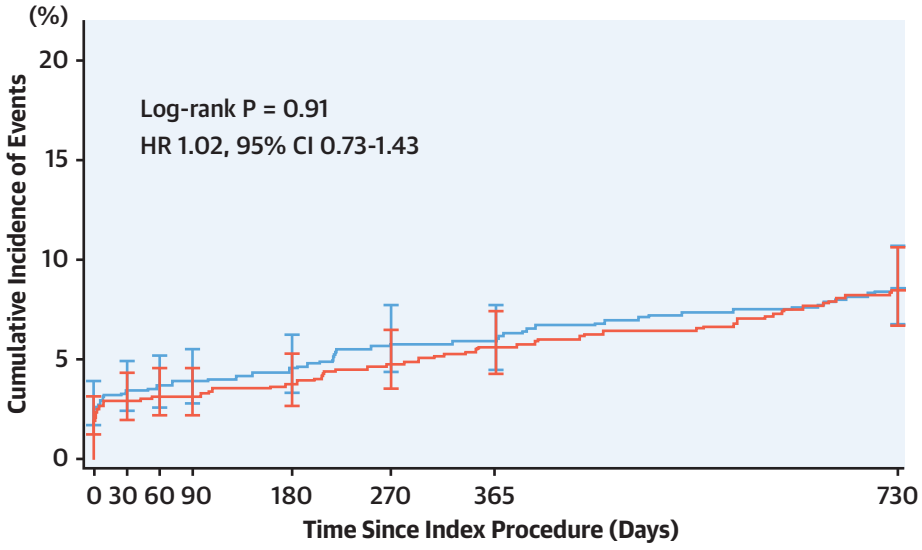
CI = confidence interval; MI = myocardial infarction; PoCE = patient-oriented composite endpoint; ST = stent thrombosis; TLR = target lesion revascularization; TVR = target vessel revascularization.

CONCEPT AND POTENTIAL BENEFIT OF FIREHAWK. The Firehawk stent has a unique design with recessed abluminal grooves facing the vessel wall, to which sirolimus and biodegradable polymer are applied (11). This stent design aims to minimize polymer volume and sirolimus drug concentrations in the vessel with the goal of reducing long-term inflammation and related clinical events, while maintaining antirestenotic effects (11). Notably, the Firehawk represents the lowest polymer volume and drug concentration among currently available biodegradable-polymer DES (9). An experimental animal study showed a low inflammation score with the Firehawk device (17), and an optical coherence tomographic substudy of the TARGET All Comers trial indicated similar healing responses 3 months after implantation of Firehawk compared with XIENCE (10).

CLINICAL EVIDENCE OF FIREHAWK. The promise of biodegradable-polymer DES as being safer than durable-polymer DES, related to the inflammatory reactions induced by permanent polymers, remains controversial (3–5). Whether the unique design of the Firehawk, with biodegradation of its polymer within 6 to 9 months, will translate into better clinical outcomes remains unanswered. Although the results with Firehawk so far are similar to those with durable-polymer DES, 2-year follow-up is likely premature and underpowered to differentiate device-based clinical outcomes, and continued evaluation will be required in the longer term. A meaningful difference in the landmark analysis of the primary device-oriented endpoint likely will require completion of 5-year follow-up.

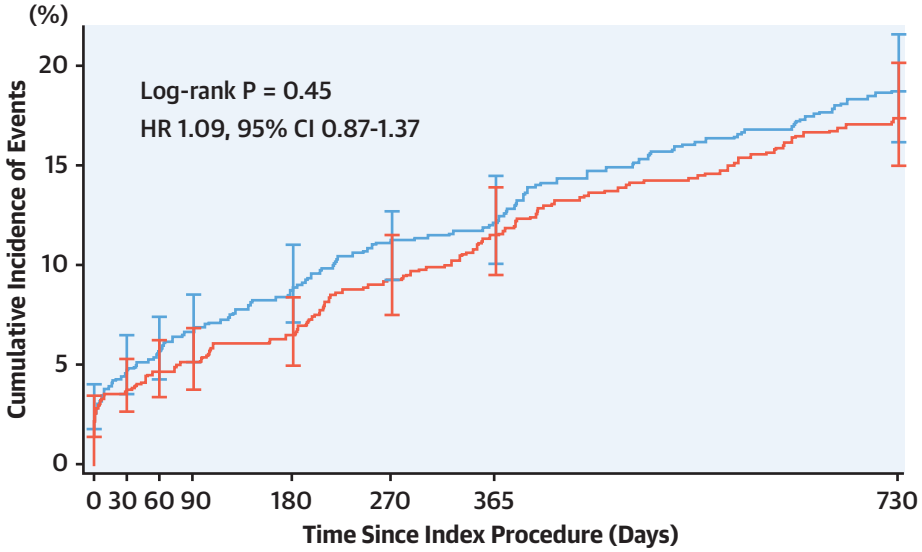
CENTRAL ILLUSTRATION **Target Lesion Failure and Patient-Oriented Composite Endpoint Up to 2 Years**

A Target Lesion Failure



Number at risk						
FIREHAWK	823	773	765	749	742	687
XIENCE	830	789	782	769	755	707

B PoCE



Number at risk						
FIREHAWK	823	753	735	711	701	628
XIENCE	830	775	763	737	718	650

FIREHAWK XIENCE

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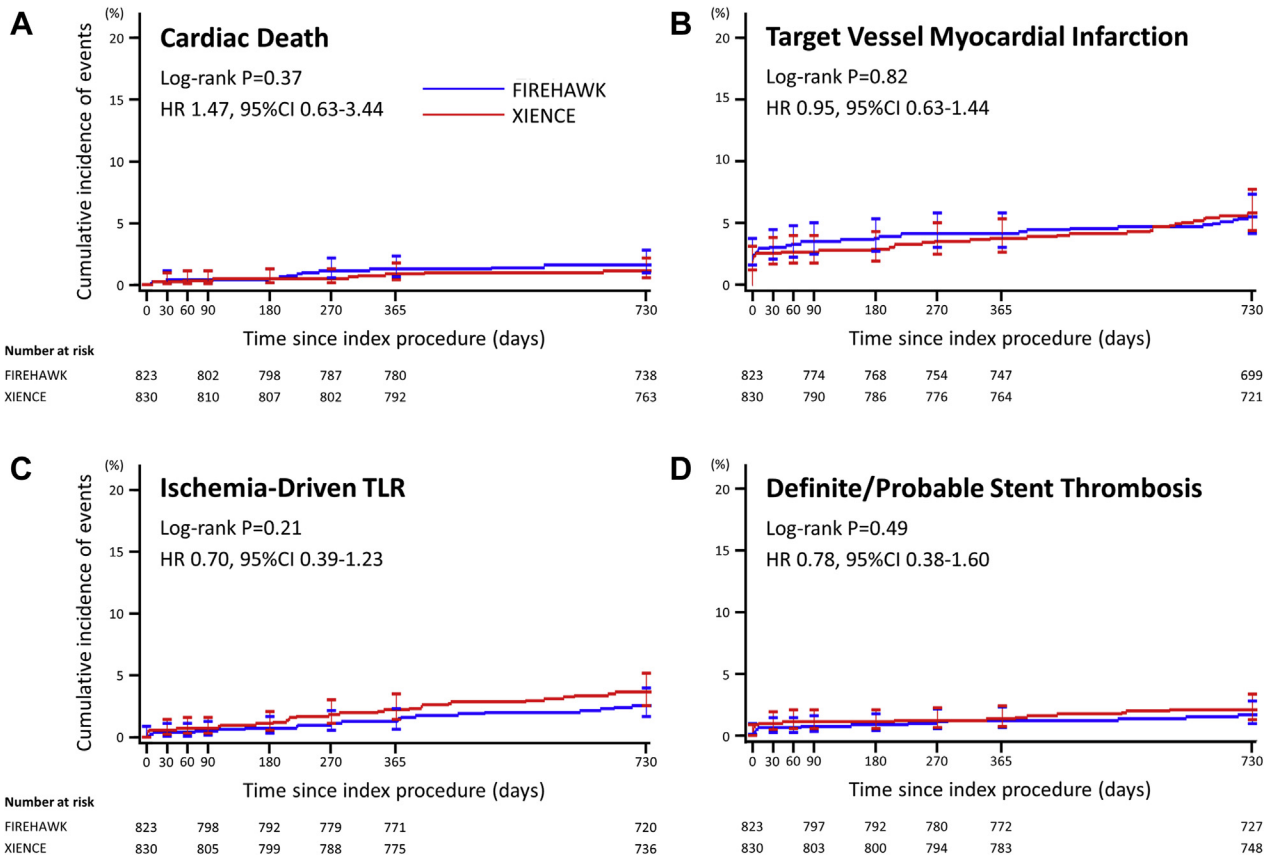
Kaplan-Meier cumulative event curves for the primary endpoint, target vessel failure **(A)**, and the patient-oriented composite endpoint (PoCE) **(B)**.
CI = confidence interval; HR = hazard ratio.

FIGURE 2 **Clinical Events Up to 2 Years**



Kaplan-Meier cumulative event curves for the individual components of target vessel failure and definite or probable stent thrombosis at 2-year follow-up. Events are cardiac death **(A)**, target vessel myocardial infarction **(B)**, ischemia-driven target lesion revascularization (TLR) **(C)**, and definite or probable stent thrombosis **(D)**. CI = confidence interval; HR = hazard ratio.

The Firehawk stent is well established to be as safe and effective at 12 months as the XIENCE DES in more than 1,000 patients in China (7,8) and more than 800 patients in Europe in the full range of complex patients (9). TARGET I randomized 458 patients with simple single coronary lesions in China to either Firehawk or XIENCE (7); the 9-month angiographic late lumen loss was comparable for the Firehawk and XIENCE stents (0.13 ± 0.24 mm vs. 0.13 ± 0.18 mm; p = 0.94), as were 12-month TLF rates (2.2% vs. 2.2%; p = 1.00) in this low-risk population (7). The TARGET II registry enrolled 730 patients treated with the Firehawk stent in more complex patients (small vessels, long lesions, and multivessel disease) with a 4.4% TLF rate at 12 months (8). The pooled patient-level analysis of TARGET I and II at 2 years confirms the low event rates with the Firehawk stent, with 4.6% TLF, 0.8% cardiac death, 2.9% target vessel MI, 1.2% TLR, and 0.1% of definite or probable stent thrombosis (18). The TARGET All Comers study, the first European patient experience with Firehawk in a post-market setting, showed that TLF at 12 months occurred in 6.1% of patients with Firehawk and in 5.9% with XIENCE (p = 0.88) (9), confirming the 1-year safety and efficacy of Firehawk previously demonstrated in China.

At 2 years, we show that Firehawk and XIENCE continue to have similar safety and efficacy, without evidence of a clinical advantage (superiority), as most other biodegradable DES have shown. We demonstrate in an all-comers population similar 2-year clinical outcomes with TLF (8.7% vs. 8.6%; p = 0.92) and definite or probable stent thrombosis (1.7% vs. 2.1%; p = 0.49) for Firehawk versus XIENCE. The SORT OUT VII trial randomized 2,525 patients to either the Orsiro biodegradable-polymer

sirolimus-eluting stent (Biotronik, Bülach, Switzerland) or the Nobori biodegradable-polymer biolimus-eluting stent (Terumo, Tokyo, Japan). Although the Orsiro stent had a lower rate of definite stent thrombosis at 12 months (0.4% vs. 1.2%; p = 0.03) (19), at 2 years there were no differences in outcomes, including definite stent thrombosis (0.8% vs. 1.4%; p = 0.14) and MI (3.6% vs. 3.7%; p = 0.93) (20). A recent meta-analysis of 16 contemporary randomized DES trials showed similar safety and efficacy of biodegradable-polymer DES regarding TLF and stent thrombosis during a mean follow-up period of 26 months compared with new-generation durable-polymer DES (21), failing to demonstrate at least at 2-year follow-up a clinical benefit.

A single study has shown better results with a biodegradable DES. The recent BIO-RESORT trial, which randomly assigned 3,514 patients to treatment with the biodegradable-polymer Orsiro sirolimus-eluting stent or Synergy everolimus-eluting stent (Boston Scientific, Marlborough, Massachusetts) or durable-polymer Resolute Integrity zotarolimus-eluting stent (Medtronic, Minneapolis, Minnesota) demonstrated comparable performance of the 3 stents, with similar TLF rates (6.6% vs. 6.8% vs. 8.3%) at 2 years. However, in the landmark analysis between 1- and 2-year follow-up, patients assigned to Orsiro had a significantly lower rate of TLF compared with the Resolute stent (1.1% vs. 2.4%; p = 0.02) (6). It is not clear whether the benefits of Orsiro are related to the biodegradable polymer or other components of its unique design (ultrathin struts for the smaller stent sizes). A pooled analysis of 3 randomized DES trials did report lower rates of definite stent thrombosis and clinically indicated TLR at 4 years with biodegradable-polymer DES implantation compared with durable-polymer DES, but the tested durable-polymer devices were first-generation DES (22). Overall results from biodegradable-polymer DES trials indicate that mid- and long-term follow-up data beyond 1 year are necessary to differentiate the safety and efficacy outcomes compared with durable-polymer DES. Continued follow-up is required to address a potential benefit of the Firehawk stent, and the TARGET All Comers study will continue to evaluate clinical outcomes up to 5 years.

STUDY LIMITATIONS. There were some limitations to the present study. First, the study was powered for the primary composite endpoint of TLF. Thus, the analysis remained underpowered to detect differences in the individual components of the primary endpoint or stent thrombosis. Second, early optical coherence tomography and angiographic follow-up substudies might contribute to increased revascularizations (9). Third, the duration of dual-antiplatelet therapy was guideline based. However, because randomization was not stratified according to duration of dual-antiplatelet therapy, between-group differences may confound outcomes between the stent platforms.

CONCLUSIONS

The 2-year follow-up of the TARGET All Comers study shows similar safety and efficacy profiles of the Firehawk and XIENCE stents. The incidence of TLF beyond 1 year was low and comparable for both treatment arms, with a low rate of stent thrombosis in a broad all-comers population.

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PERSPECTIVES

WHAT IS KNOWN? Outcome data beyond 1 year with the abluminal groove-filled biodegradable-polymer sirolimus-eluting Firehawk DES have not been reported in an all-comers population.

WHAT IS NEW? The TARGET All Comers study confirms similar safety and efficacy profiles of the Firehawk stent compared with the XIENCE stent at 2 years.

WHAT IS NEXT? Further long-term follow-up assessment and real-world data are warranted to address potential benefits of the Firehawk stent.

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KEY WORDS clinical outcome, drug-eluting stent, everolimus-eluting stent, Firehawk

APPENDIX For supplemental figures and a supplemental table, please see the online version of this paper.