Rapamycin-Eluting Coronary Stent for PCI: The TARGET IV Trial

A review of the TARGET IV trial evaluating the Firehawk rapamycin-eluting cobalt chromium coronary stent system. Can this new stent increase healing time, reduce adverse events, and eliminate the need for prolonged dual antiplatelet therapy?

By Christiana O. Oshotse, BA, and Robert W. Yeh, MD, MSc, MBA

The options for mechanical interventions used in percutaneous coronary intervention (PCI) have evolved from balloon angioplasty in the 1970s to 1980s to the bare-metal stents (BMS) introduced in 1986 that provided permanent scaffolding to the opened vessel, thus addressing the issue of vessel recoil after angioplasty.[1] In 2000, drug-eluting stents (DES) were developed, which employed antiproliferative drugs to coat stents and inhibit cell growth after stent implantation.[2-4] DES greatly reduced the risk of neointimal hyperplasia and associated restenosis, representing a critical breakthrough in offering sustained benefits for patients.[5,6]

The first generation of DES addressed the high rates of restenosis with BMS by applying a polymer onto thick stainless-steel metal stents that distributed paclitaxel or sirolimus to reduce the neointimal proliferative response observed with BMS.[1,2,7] First-generation DES combined drug coatings with durable polymer—eg, SIBS (poly[styrene-block-isobutylene-block-styrene]), PEVA (poly[ethylene-co-vinyl acetate]), and PBMA (poly[n-butyl methacrylate])—that stabilized the drugs eluted from the stents.[8]

Taxus (Boston Scientific Corporation), comprising paclitaxel and SIBS, and Cypher (Cordis), comprising sirolimus, PEVA, and PBMA, were two first-generation stents with strut thickness > 130 mm and durable polymer coating > 10 mm. They significantly reduced restenosis rates and improved outcomes compared to BMS. However, the risks of late stent thrombosis clouded the success of DES, and efforts to design newer stents that allowed for more rapid endothelialization were undertaken to reduce the risk as well as shorten the associated mandatory duration of dual antiplatelet therapy (DAPT) to prevent stent thrombosis. During this time, studies exploring the efficacy of DAPT use after stent implantation had positive results and explored strategies to prolong DAPT use to limit stent thrombosis, all of which led to national guidelines for PCI to encourage DAPT use.[9-12]

Subsequent iterations of DES, comprising second-generation DES, improved on efforts to reduce rates of restenosis, neointimal hyperplasia, and inflammation in patients with thinner metallic platforms (eg, stainless steel, cobalt-chromium, platinum-chromium alloy). These were accompanied by more varied stent coatings (eg, biodegradable polymer, polymer-free coating, bioabsorbable coating, nanocoating) and served as a drug carrier for antiproliferative and immunosuppressant drugs (eg, everolimus, zotarolimus, biolimus, hybrid drugs) released at varying drug combinations and kinetics to the stented site.[4,6,7,13-15] Lower rates of thrombosis are achieved with these second-generation DES, even as a shift toward more truncated DAPT durations occurred, in part due to the recognition that bleeding on DAPT is common and harmful.[16-20] Trial data over the years continue to confirm that thinner struts with improved and varied stent coatings that provide reduced contact with artery wall and targeted drug delivery can reduce inflammation, neointimal hyperplasia, thrombosis, and resultant mortality in patients with stents.

THE NOVEL FIREHAWK STENT SYSTEM

Despite major improvements in stent mechanics, there remains a need to accelerate endothelization after stent implantation to prevent the continually observed late stent thrombosis and requirement for DAPT that contribute to existing unfavorable patient outcomes. Contemporary strategies for antiplatelet thearpy rely on individualizing treatment based on bleeding and ischemic risk, but they nevertheless continue to be associated with significant bleeding risks, drug interactions, and increased cost to patients. It remains necessary to improve on the factors of stent design that persist in the predominantly used second-generation durable polymer DES and contribute to persistent stent-related failure over the long term. Strut design that decreases turbulent flow, stent coating that diminishes immune response provocation and late "catch-up" stenosis, and proper stent deployment are key areas to address.

The novel Firehawk stent is designed by MicroPort and currently used in China, the European Union, Korea, India, Brazil, Colombia, Belarus, Egypt, and Saudi Arabia. The stent design is intended to improve healing and reendothelialization to prevent stent thrombosis. It is being studied in the TARGET trials, with the most recent TARGET IV trial evaluating its use in North American and European patient populations.

Firehawk is a third-generation, cobalt-chromium, balloon-expandable stent with a biodegradable polymer housed in abluminal grooves and mounted on a rapid exchange delivery catheter system. The biodegradable polymer delivers rapamycin to reduce the proliferative response and eventually degrades to leave only the implanted metallic stent. The stent is designed to minimize polymer volume and antiproliferative drug concentration to reduce inflammation and hypersensitivity reactions. The Firehawk's design aims to prevent coating damage and drug loss during moments of rupture or high-pressure postdilatation during delivery.

PREVIOUS AND ONGOING STUDY EVALUATIONS OF FIREHAWK

The Firehawk stent has been evaluated in > 35,600 patients worldwide.[21-34] Thus far, initial studies of the stent system have been completed in 1,007 patients across three completed trials in China—one first-in-human feasibility study (N = 21), the TARGET I randomized trial (N = 510), and the TARGET II clinical trial (N = 716). Each study analyzed clinical and angiographic data and conducted individual follow-up for ≥ 12 months.

TARGET I trial evaluated the Firehawk with two approaches. The first was a prospective, multicenter, randomized controlled trial (RCT) (N = 458) evaluating the stent's safety and efficacy against the Xience V stent (Abbott). Patients were randomized 1:1, with a primary endpoint of in-state late lumen loss (LLL) at 9 months. The second approach employed a single-arm registry (N = 50) to evaluate the long Firehawk stents (33 and 38 mm). In the RCT, the Firehawk was found to meet the noninferiority criteria for in-stent LLL at 9 months, with acceptable clinical success, restenosis rates, stent thrombosis, and target lesion failure (TLF) during clinical follow-up at 9 months, 1 year, and annually up to 5 years.[34]

The TARGET II registry (N = 730) employed a prospective, multicenter, open-label design to primarily evaluate TLF at 12 months in patients who received the Firehawk. Clinical follow-up at 1 and 6 months and annually up to and including 5 years showed that TLF occurred in 4.4%

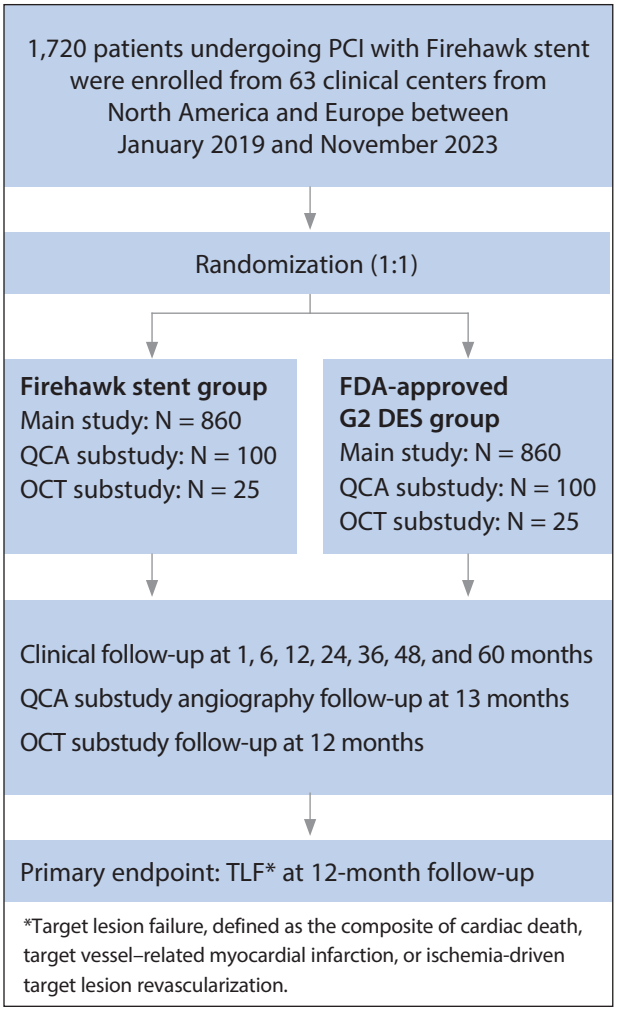

Figure 1. Enrollment, randomization, and clinical follow-up parameters for the TARGET IV trial. OCT, optical coherence tomography; QCA, quantitative coronary angiography.

TABLE 1. SELECTED INCLUSION AND EXCLUSION CRITERIA FOR TARGET IV

Selected Inclusion Criteria	
• Patients with an indication for PCI including angina (stable or unstable), silent ischemia (in absence of symptoms, a visually estimated target lesion diameter stenosis of ≥ 70%, a positive noninvasive stress test, or a positive coronary physiology test [eg, FFR ≤ 0.80 or iFR < 0.90 24 h and peaked enzyme levels]) • For STEMI, the time of presentation to first treating hospital, whether transfer facility or study hospital, must be > 24 h prior to randomization with enzyme levels (CK-MB or troponin) demonstrating that either or both enzyme levels have peaked • Target lesion(s) must be located in a native coronary artery with visually estimated diameter of ≥ 2.25 to ≤ 4 mm and up to 44 mm in length • Coronary anatomy deemed likely to allow delivery of a study device to the target lesion(s) • Complex lesions are allowed, including calcified lesions (lesion preparation is allowed and strongly recommended with current approved devices such as scoring/cutting balloon and rotational/orbital atherectomy), multivessel disease, chronic total occlusion, bifurcation lesions (except planned dual stent implantation), ostial lesions, tortuous lesions, and protected left main lesions • Overlapping stents are allowed	
Selected Exclusion Criteria	
Clinical exclusion criteria	• STEMI within 24 h of initial time of presentation to first treating hospital, whether transfer facility or study hospital or enzyme levels (either CK-MB or troponin) that have not peaked • Hemoglobin < 10 g/dL • Platelet count < 100,000 cells/mm^3 or > 700,000 cells/mm^3 • White blood cell count < 3,000 cells/mm^3 • Clinically significant liver disease • Active peptic ulcer or active bleeding from any site • Other serious medical illness with a life expectancy < 24 mo (eg, cancer, severe heart failure, severe lung disease)
Angiographic exclusion criteria	• Unprotected left main interventions • Bifurcation lesions with intended dual stent implantations • DES restenotic lesions • Prior PCI in the target vessel in the 12 mo prior to enrollment • Any lesion in the target vessel that is likely to require PCI within 12 mo • Stent lengths > 36 mm for diameters 2 mm and 2.25 mm (ie, very long thin stents) • Lesion with intended stent implantation ≥ 3

Abbreviations: CK-MB, creatine kinase-myocardial band; DES, drug-eluting stent; IFR, instantaneous wave-free ratio; FFR, fractional flow reserve; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

(32 of 730) of patients, which is lower than the objective performance criteria. Metrics for clinical success specifically defined for the study were also achieved at 96.8% (707 of 730).[32]

TARGET All Comers (N = 1,653) was a prospective, multicenter, randomized controlled, open-label, noninferiority trial in an "all-comers" patient population at 21 investigational sites in Europe. Patients were randomized 1:1 to Firehawk or the Xience family of everolimus-eluting stents. The trial was designed to assess the safety and effectiveness of Firehawk for treatment of patients with atherosclerotic lesion(s) in coronary arteries ≥ 2.25 and ≤ 4 mm in diameter with minimal exclusion criteria in a real-world consecutive population. The trial enrolled 1,653 patients and demonstrated comparable rates of TLF between the Firehawk and Xience out to 5 years.[28]

Subsequent and ongoing studies have focused on evaluating the complexities of coronary artery disease and the potential of Firehawk to provide efficacious long-term care in patients through the TARGET DAPT study, TARGET SAFE trial, and TARGET FIRST, among other country-specific trials.[35-37]

TARGET IV NORTH AMERICAN DESIGN

These promising earlier studies and the subsequent update of Firehawk across multiple countries engen-

dered a desire to understand the stent's impact in encouraging quicker reendothelialization and reducing stent thrombosis in a North American population.

The TARGET IV North American trial is a prospective, multicenter, single-blind, 1:1 randomized, noninferiority trial comparing Firehawk (treatment) with commercially approved second-generation DES (control) (Figure 1). The trial was designed to enroll up to approximately 1,720 patients with clinical indications for PCI. The estimated primary completion date is 2024, and the study completion date is 2027. Key enrollment criteria are detailed in Table 1. Patients were enrolled from January 2019 to November 2021. Treatment allocation was stratified by centers and presence of diabetes mellitus and acute coronary syndrome versus non–acute coronary syndrome indication. The trial completed enrollment and is now in the follow-up phase. The trial was designed to support a United States premarket application.

Two substudies will be employed, with the first consecutive 200 patients (approximately) enrolled in the angiographic quantitative coronary angiography study and the first consecutive 50 patients (approximately) enrolled in the optical coherence tomography study.

The primary endpoint of the main study will gauge TLF at 12 months, with secondary endpoints measured at 30 days, 6 months, and annually up to and including 5 years to evaluate TLF, target vessel failure, and major adverse cardiac events, among other metrics. Performance measures will further investigate the device, lesion, and procedure success as well.

POTENTIAL IMPACT FOR PATIENTS AND ON PRACTICE

The first three TARGET trials of the Firehawk stent have shown promising results in patient populations in China, which has led to an increased use of the Firehawk stent as well as positive outcomes for these patients in > 40 countries across the European Union, Korea, India, Latin America, Saudi Arabia, and more.

Results from the TARGET IV North American trial is intended to be used to support FDA approval for the use of Firehawk in the United States. No Chinese-manufactured stents are currently available in the North America. Current rates of subsequent early stent thrombosis occur at an expected rate of approximately 1%, and late stent thrombosis occurs at 0.4% to 0.6% annually up to 4 years. Despite these low rates, stent thrombosis is associated with a mortality ranging from 5% to 45% after stent implantation, and it remains a clinical concern.[5,13,38] Although the TARGET IV trial is not powered to demonstrate superiority over existing alternatives, any stent that can potentially promote more rapid healing and demonstrate reduced rates of stent thrombosis or require shorter durations of DAPT would be a welcome addition to the current clinical landscape. ■

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Christiana O. Oshotse, BA
Medical Student
Harvard Medical School
Boston, Massachusetts
christianaoshotse@hms.harvard.edu
Disclosures: None.

Robert W. Yeh, MD, MSc, MBA
Section Chief, Interventional Cardiology
Beth Israel Deaconess Medical Center
Director, Richard A. and Susan F. Smith Center for Outcomes Research
Katz-Silver Family Professor of Medicine
Harvard Medical School
Boston, Massachusetts
ryeh@bidmc.harvard.edu
Disclosures: Consultant to Abbott Vascular, Boston Scientific Corporation, and Medtronic; one of the national Co-Principal Investigators for the TARGET IV North American study.