Journal of the Society for Cardiovascular Angiography & Interventions 1 (2022) 100511

Contents lists available at ScienceDirect

Journal of the Society for Cardiovascular Angiography & Interventions

journal homepage: www.jscai.org

Study Design

Design and Rationale of Targeted Therapy With a Sirolimus-Eluting, Biodegradable Polymer Coronary Stent in Chronic Total Occlusions (TARGET CTO): A Multicenter, Open-Label, Randomized Noninferiority Trial

Yaling Han, MD, PhD [a,*], Geng Wang, MD [a], Yi Li, MD [a], Ming Zheng, MD [b], Ruifen Cao, MD [b], Ruiyan Zhang, MD [c], Shaoliang Chen, MD [d], Jian'an Wang, MD [e], Yitong Ma, MD [f], Zhiqi Sun, MD [g], Xueqi Li, MD [h], Xi Su, MD [i], Wen Lu, MD [j], Yawei Xu, MD [k], Ernest Spitzer, MD [l,m], Xue Li, MD [n], Fucheng Sun, MD [o]

[a] *Department of Cardiology, General Hospital of Northern Theater Command, Shenyang, China;* [b] *Shanghai MicroPort Medical (Group) Co, Ltd, Shanghai, China;* [c] *Department of Cardiology, Ruijin Hospital of Shanghai Jiao Tong University School of Medicine, Shanghai, China;* [d] *Department of Cardiology, Nanjing First Hospital, Nanjing, China;* [e] *Department of Cardiology, the Second Affiliated Hospital Zhejiang University School of Medicine, Hangzhou, China;* [f] *Department of Cardiology, the First Hospital of Xinjiang Medical University, Urumqi, China;* [g] *Department of Cardiology, DaQing Oilfield General Hospital, DaQing, China;* [h] *Department of Cardiology, the Fourth Affiliated Hospital of Harbin Medical University, Harbin, China;* [i] *Department of Cardiology, Wuhan Asia Heart Hospital, Wuhan, China;* [j] *Department of Cardiology, Xuzhou Central Hospital, Xuzhou, China;* [k] *Department of Cardiology, Shanghai Tenth People's Hospital, Shanghai, China;* [l] *Cardialysis, Rotterdam, the Netherlands;* [m] *Department of Cardiology, Thoraxcenter, Erasmus University Medical Center, Rotterdam, the Netherlands;* [n] *Department of Cardiology, Tangdu Hospital of Air Force Military Medical University, Xian, China;* [o] *Department of Cardiology, Beijing Hospital, Beijing, China*

ABSTRACT

Background: Treatment of chronic total occlusions (CTOs) is referred to as the last frontier of percutaneous coronary interventions and is currently performed in 10% to 20% of procedures. Improved outcomes with newer generation drug-eluting stents require further research.

Methods: The TARGET CTO trial (NCT03040934) is a prospective, multicenter, randomized, noninferiority trial that plans to randomize 196 subjects (1:1) to either a newer-generation sirolimus target-eluting stent or an everolimus-eluting stent. Patients are candidates if they present with at least 1 CTO lesion in a native coronary artery with a diameter of ≥2.50 mm to ≤4.00 mm and a length of <100 mm. In addition, 44 subjects will participate in an optical coherence tomography (OCT) substudy. Clinical follow-up is planned up to 5 years after stent implantation. Angiographic follow-up is planned at 12 months, whereas OCT will be obtained after the procedure, at 3 and 12 months. The primary end point is in-stent late lumen loss by quantitative coronary angiography at 12 months. The key secondary end point is neointimal thickness by OCT at 3 months. Imaging end points are assessed by an independent core lab. Clinical end points are adjudicated by an independent clinical events committee.

Conclusion: The TARGET CTO trial compares a sirolimus target-eluting stent with an everolimus-eluting stent for management of CTOs according to contemporary interventional practices. The primary angiographic end points will be reported at 12 months and clinical follow-up will continue for up to 5 years.

Introduction

Chronic total occlusions (CTOs) refer to coronary atherosclerotic lesions with 100% occlusion of the coronary lumen that persists for at least 3 months due to organized thrombus. CTOs are found in up to one-third of patients diagnosed with coronary atherosclerosis by coronary angiography, but <8% undergo a percutaneous coronary intervention (PCI) procedure, amounting to 10% to 20% of all PCIs.[1] Treatment of CTOs is technically complex, has a lower immediate success rate, and a higher incidence of reocclusions and restenosis. Thus, CTOs are considered one of the biggest challenges in coronary interventions.[2]

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; CTO, chronic total occlusion; DES, drug-eluting stent; ESC, European Society of Cardiology; ICF, informed consent form; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography.

Keywords: chronic total occlusion; drug-eluting stent; optical coherence tomography; percutaneous coronary intervention; quantitative coronary angiography.

* Corresponding author: : hanyaling@263.net (Y. Han).

https://doi.org/10.1016/j.jscai.2022.100511

Received 12 July 2022; Received in revised form 13 September 2022; Accepted 21 September 2022

Available online 17 October 2022

Randomized data on CTO interventions are scarce, and societal guidelines consistently indicate a Class IIa recommendation.[3,4] Current evidence suggests that PCI of CTOs with new-generation drug-eluting stents (DESs) may benefit patients by reducing myocardial ischemia and by improving long-term survival.[4] Novel coronary stent platforms may prove advantageous and need to be tested in this specific indication.[4] The theoretical benefits require prospective confirmation, as recently highlighted in the Primary Stenting of Occluded Native Coronary Arteries IV trial, where a novel sirolimus-eluting stent platform did not reach noninferiority compared with an established everolimus-eluting stent (EES) platform.[5]

The Firehawk rapamycin target-eluting cobalt chromium coronary stent system (Firehawk stent system, Shanghai MicroPort Medical Group Co, Ltd) is a new-generation balloon-expandable L605 cobalt chromium stent with abluminal grooves containing a biodegradable polymer that provides controlled release of the antiproliferative medicinal substance rapamycin (sirolimus). The polymer is biodegradable, leaving only the metallic stent as a permanent implant. The stent is mounted on a rapid-exchange delivery catheter system. The Firehawk stent received registration approval from the China Food and Drug Administration in December 2014 and received the CE mark in January 2015.

This device was tested in a large, randomized all-comers coronary intervention trial against the XIENCE platform (Abbott Vascular), a durable polymer everolimus-eluting coronary stent considered as the industry standard. The prospective multicenter randomized post market trial to assess the safety and effectiveness of the Firehawk rapamycin target eluting cobalt chromium coronary stent system for the treatment of atherosclerotic lesions (TARGET AC) included 1653 patients, and no differences were observed for the primary end point of target lesion failure (a composite of cardiac death, target vessel myocardial infarction, or ischemia-driven target lesion revascularization) up to 2 years of follow-up (8.7% in the Firehawk group vs 8.6% in the XIENCE group; $P = .92$).[6] TARGET AC did include a subgroup of patients presenting with coronary occlusions for >72 hours; however, these were not classed prospectively as CTOs, which require evidence of occlusion for at least 3 months, and the sample was limited (47 in the Firehawk arm and 51 in the XIENCE arm, data on file). It is consequently relevant to evaluate the use of the Firehawk stent in CTOs.

Objectives

To assess the safety and effectiveness of the Firehawk sirolimus target-eluting coronary stent system with abluminal grooves containing a biodegradable polymer compared with the XIENCE EES system in the treatment of CTOs by coronary angiographic follow-up and intracoronary OCT. This trial also adds to the external validity of the findings of the TARGET AC trial specifically in patients with CTOs.

Trial design

The TARGET CTO trial (NCT03040934) is a prospective, multicenter, randomized, noninferiority trial (Central Illustration). It plans to recruit 196 subjects (all participants will be randomized to Firehawk or XIENCE EES at a ratio of 1:1) with a CTO in a native coronary artery with a diameter of ≥2.50 mm to ≤4.00 mm (by visual estimate) and a length of <100 mm (by visual estimate) at approximately 12 study sites in China. The first 44 consecutive subjects who provided informed consent will participate in a substudy that includes OCT assessment immediately after the baseline procedure, at 3 months, and at 12 months after the baseline procedure. The OCT substudy will be performed at 3 to 5 preselected sites. All subjects will be followed up at 30 days, 3 months, 6 months, 12 months, and 2 to 5 years after stent implantation. All subjects will undergo angiographic follow-up at 12 months.

The TARGET CTO trial complies with the principles outlined in the International Committee on Harmonization of Good Clinical Practice guidelines, the Declaration of Helsinki, International Organization for Standardization 14155, the Norms of the Quality Management for the Clinical Trials of Medical Devices, and the principles of the Ethics Committee approving the study.

Materials and methods

Study setting

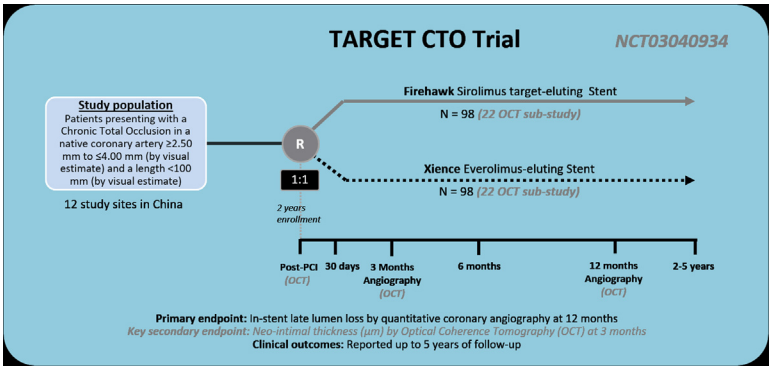
Data will be collected from approximately 12 interventional centers in China. A list of the participating centers is provided in the Supplementary Table 1.

Screening process and eligibility

The clinical and angiographic eligibility criteria for the TARGET CTO study are shown in Tables 1 and 2. Subjects should meet all inclusion criteria and not meet any exclusion criterion before entering the trial.

Informed consent

Subjects who meet the clinical eligibility criteria are required to sign the study's informed consent form (ICF) approved by the ethics committee before any study-specific tests or procedures are performed. Before signing, the investigator must allow the subject to have sufficient time to read the ICF and should answer questions from the subject. The study staff should explain to the subject that even if the subject agrees to participate in this study and signs the ICF, the cardiac catheterization test may also reveal that the subject is not suitable for this study.



Central Illustration. TARGET CTO study design summary.
CTO, chronic total occlusion; OCT, optical coherence tomography.

Table 1. Inclusion criteria for the TARGET CTO trial

Clinical inclusion criteria
The subjects must at least 18 y old.
Before implementing any specific tests or procedures in the trial, subjects (or legal guardians) should understand the testing requirements and procedures and provide written informed consent.
Subjects plan to undergo percutaneous coronary intervention and drug-eluting stent implantation.
Subjects with symptomatic coronary artery disease or proven asymptomatic ischemia (including NST-ACS; stable coronary artery disease; and STEMI older than 3 mo).
Subjects are eligible candidates for CABG.
The left ventricular ejection fraction measured by ultrasonography within 30 d before enrollment is ≥35%.
Subjects are willing to receive all subsequent evaluations required by the trial protocol.
Angiographic inclusion criteria
The target lesion must be located in a de novo native coronary artery with reference vessel diameter of ≥2.50 mm to ≤4.00 mm, as visually measured.
Target lesions must be <100 mm in length (visual estimate), and the planned number of implanted stents is no more than 4.
Target lesions must be visually complete occlusions and longer than 12 wk.
It must be possible to successfully cross and predilate the target lesions.

CABG, coronary artery bypass graft; CTO, chronic total occlusion; NST-ACS, non-ST-elevation acute coronary syndrome; STEMI, ST-elevation myocardial infarction.

Randomization

If the subject who meets the clinical eligibility criteria is found to meet an exclusion criterion during the angiographic eligibility assessment, the subject is considered to have failed screening and should not be randomized or receive the study device and should not be followed up after the procedure, according to the protocol. If the subject is found to meet the inclusion criteria during the diagnostic angiography phase of the procedure and the target lesion is amenable to revascularization and successful predilatation, the subject is considered eligible for randomization. This study uses the interactive web response system to assign subjects to different study groups. After the subject is successfully randomized, it is considered that the subject has entered this study. Eligible subjects will be randomized to the Firehawk group and the XIENCE group at a 1:1 ratio.

Interventions

Antithrombotic medications

Based on the guidelines of the American College of Cardiology (ACC)/American Heart Association (AHA)/Society for Cardiovascular Angiography and Interventions (SCAI)[7,8] and the European Society of Cardiology (ESC),[9,10] subjects should undergo dual antiplatelet therapy with aspirin and clopidogrel/ticagrelor to minimize the risk of thrombosis. During the procedure, subjects must use heparin or other anticoagulants (such as bivalirudin or enoxaparin). If heparin is used, it is recommended to maintain an activated clotting time of >250 seconds throughout the procedure. If the blood is anticoagulated with enoxaparin or bivalirudin, the anticoagulation level should be monitored according to the routine conditions of the laboratory of the hospital. The investigator may decide to use tirofiban at their own discretion.

Post-PCI medical therapy

Subjects who receive at least 1 study stent are treated based on the ACC/AHA/SCAI and ESC guidelines.[7,9,10] After the baseline procedure, subjects must use P2Y12 receptor inhibitors (clopidogrel/ticagrelor) (the recommended dose of clopidogrel is 75 mg per day, and ticagrelor 90 mg each time, twice daily) for at least 12 months. Subsequently, the P2Y12 inhibitor treatment is decided by the physician. It is recommended that after stent implantation, 100 mg of aspirin should be administered every day for an indefinite period. In addition to dual antiplatelet therapy, subjects are advised to receive the best drug treatment (including statins and β-blockers) to improve treatment outcomes.

Outcomes

The primary end point of the TARGET CTO trial is in-stent late lumen loss at 12 months after the baseline procedure. The key secondary end point is neointimal thickness (μm) measured by OCT at 3 months after the baseline procedure. The complete list of clinical, angiographic, and OCT-based end points are listed in Table 3.

Data collection

Data collection and follow-up

All enrolled and treated subjects will be evaluated at 30 days, 3 months, 6 months, 12 months, 2 years, 3 years, 4 years, and 5 years after the procedure according to the schedule of assessment (see Supplementary Table 2). Subjects who are enrolled but have not received the study stent will be followed up until 12 months only. The protocol-specified follow-up assessments can be made in the form of telephone interviews or hospital visits in accordance with local medical routine and the subject's mobility. At each visit required by the protocol, the study site staff should answer all the relevant questions raised by the subject in addition to the assessment required by the protocol. After all subjects have completed the 12-month follow-up, the study is considered to have reached the primary end point.

Angiographic assessments

During the baseline procedure, all subjects undergo angiographic assessment according to the standard of care. Angiographic follow-up is performed at 12 months. Subjects requiring reintervention of the target vessel within the 5-year follow-up period are evaluated by angiography according to the standard of care. Angiographic and OCT images are submitted to the independent angiographic and OCT core laboratory for central qualitative and quantitative analysis. Collection of angiographic images of both target and nontarget vessel reinterventions is required.

OCT substudy follow-up

This evaluation is only applicable to the subset of subjects undergoing OCT assessment at the 3-month follow-up at the clinical sites selected to participate in the OCT substudy. The first 44 consecutive subjects who provide informed consent undergo OCT assessment immediately after the baseline procedure, at 3 and12 months. The OCT substudy will be performed at 3 to 5 preselected sites. With a commercially available OCT system, an automated pullback through the stented segment will be performed according to the local standard of care. The angiography and OCT images of the target lesion will be sent to the OCT core laboratory as instructed for analysis.

Statistical methods

The trial is powered to test noninferiority for the primary end point and the key secondary end point. For the primary end point, the trial assesses the noninferiority for in-stent late loss of the Firehawk stent compared with the XIENCE EES at the 12-month angiography follow-up. In the Randomized Comparison of XIENCE V Everolimus-Eluting and TAXUS Paclitaxel-Eluting Stents (SPIRIT) I and II trials, the mean in-stent late lumen loss (LLL) for EES during follow-up was 0.10 and 0.11 mm, respectively.[11,12] For the Firehawk stent, the Prospective Multi-center Randomized Trial Assessing the Safety and Effectiveness of Biodegradable Polymer Target Release

Table 2. Exclusion criteria for the TARGET CTO trial

Clinical exclusion criteria
Subjects who have recently experienced STEMI (within 12 wk).
Subjects with hemodynamic instability (including Killip greater than Grade 2 or NYHA greater than Grade 2).
Subjects who have a ventricular aneurysm larger than 3.0 × 2.0 mm or intracardiac thrombus as shown by echocardiography within 30 d before enrollment.
Subjects who have already received or are waiting for organ transplantation.
Subjects who are receiving or scheduled to receive chemotherapy within 30 d before or after the baseline procedure.
Subjects are undergoing chronic (≥72 h) anticoagulant therapy (such as heparin and coumarin) for indications other than acute coronary syndrome.
Subjects with abnormal counts of platelets and white blood cells.
Subjects who have confirmed or suspected liver disease, including laboratory results of hepatitis.
Subjects undergoing dialysis therapy or with a serum creatinine level of >3.0 mg/dL.
Subjects with active peptic ulcer, active gastrointestinal bleeding, or other bleeding diathesis or coagulopathy.
Subjects with cerebral vascular accident or transient ischemic attack in the past 6 mo or with permanent nerve defects leading to incompliance with trial protocol.
Subjects who have received any type of PCI treatment for target vessel (including collateral branches) (eg, balloon angioplasty, stent, and cutting balloon) within 12 mo prior to the baseline procedure.
Proximal or distal target lesion vessel within 10 mm (visual estimate) has received any type of PCI (such as balloon angioplasty, stent, and cutting balloon) at any time prior to the baseline procedure.
Nontarget lesion vessels have received any type of PCI (such as balloon angioplasty, stent, and cutting balloon) within 24 h prior to the baseline procedure.
Subjects who are scheduled to receive PCI or CABG of target vessels within 1 y after the baseline procedure.
Patients who have been treated with intracoronary brachytherapy at any time previously.
Subjects who are allergic to investigational stent system or concomitant drugs required in the protocol (such as everolimus, rapamycin, or structurally related compounds; fluorine-containing polymers; thienopyridine or aspirin; contrast agent; acrylic acid; stainless steel; chromium; nickel; iron; and tungsten).
Subjects with other serious medical conditions (such as cancer and congestive heart failure), which may reduce the expected life expectancy to within 12 mo.
Subjects who currently have drug abuse (such as alcohol, cocaine, and heroin).
Subjects who plan to undergo procedures that may lead to nonconformity with the protocol or confusion in data interpretation.
Subjects who are participating in another investigational drug or device clinical trial in which the primary end point has not yet been reached or intend to participate in another investigational drug or device clinical trial within 12 mo after the baseline procedure.
Subjects who are known to plan to have children within 12 mo after the baseline procedure. (For women with child-bearing potential, it is necessary to agree to use reliable contraceptive methods throughout 12 mo from screening to the baseline procedure).
Pregnant or breast-feeding subjects (women who may become pregnant must receive a pregnancy test within 7 d prior to the baseline procedure).
Angiographic exclusion criteria
Subjects with target lesions meeting the following criteria:
• During the baseline procedure, more than 2 de novo lesions are treated.
• Left main coronary artery (LMCA).
• Subjects with target lesions involving bifurcation (stenosis of branch blood vessels of >70%), with a branch vessel diameter of ≥2.5 mm and branch lesion length more than 5 mm requiring bifurcation stent implantation.
• Located in a saphenous vein graft or an arterial graft.
• Entering through a saphenous vein graft or an arterial graft.
• In-stent restenosis.
Subjects with unprotected LMCA disease (diameter stenosis > 50%)
Subjects with protected LMCA disease (diameter stenosis > 50% at the left main coronary artery and left coronary artery bypass procedure) as well as target lesions located in the left anterior descending and left circumflex arteries.
Subjects with other clinically significant lesion(s) at target vessels, requiring revascularization within 12 mo after the baseline procedure.

CABG, coronary artery bypass graft; CTO, chronic total occlusion; LMCA, left main coronary artery; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

Table 3. End points in the TARGET CTO trial

Primary end point (angiographic)
In-stent late lumen loss at 12 mo
Key secondary end point (OCT)
Neointimal thickness (μm) by OCT at 3 mo
Clinical end points
Target vessel failure rate
Ischemia-driven target lesion revascularization rate
Ischemia-driven target vessel revascularization rate
Target lesion failure rate
Incidence of MI (including Q-wave MI and non Q-wave MI)
Cardiac death rate
Noncardiac death rate
All-cause death rate
Cardiac death or MI incidence
Stent thrombosis (definite and probable stent thrombosis per Academic Research Consortium definition)
Angiographic end points (at 12 months)
In-stent and in-segment percent diameter stenosis (%)
In-stent late loss (mm) (the efficacy end point with statistical power)
In-segment late loss (mm)
In-stent and in-segment binary restenosis rate
In-stent and in-segment minimum lumen diameter (MLD)
OCT end points (at 3 and 12 mo)
Mean neointimal thickness (μm) (the efficacy end point at 3 mo with statistical power)
Average diameter/area of the smallest stent (mm/mm^2)
Average diameter/area of the smallest lumen (mm/mm^2)
Lumen volume (mm^3)
Stent volume (mm^3)
Mean neointimal hyperplasia area/volume (mm^2/mm^3)
In-stent neointimal hyperplasia volume obstruction (%)
Malapposed strut rate (%)
Uncovered strut rate (%)
Malapposed and uncovered strut rate (%)
Perioperative end points
Device implantation success rate
Clinical procedural success rate
MLD (QCA)
Immediate lumen attainment (QCA)

MI, myocardial infarction; MLD, minimum lumen diameter; OCT, optical coherence tomography; QCA, quantitative coronary arteriography.

Rapamycin-Eluting STent vs XIENCE V Everolimus-Eluting Stent for the Treatment of Coronary Artery Disease (TARGET I) and TARGET first-in-man trials showed in-stent LLL ranging from 0.13 to 0.16 mm.[13,14] Therefore, it was assumed that both EES and sirolimus-eluting stent had the same mean values of 0.20 mm for in-stent LLL at the 12-month angiography follow-up, and an SD of 0.50 mm was also assumed for both groups. With an expected in-stent LLL at 12 months of 0.20 mm for both platforms with a noninferiority margin of 0.20 mm, a one-sided α level of 0.05, 80% power, and a 12-month attrition rate of 20%, the study requires a total of 196 randomized patients (98 in each group).

For the key secondary end point by OCT, ie, neointimal thickness of the stent measured at 3 months, noninferiority testing and superiority testing will be adopted sequentially. In the TARGET first-in-man trial, the mean neointimal thickness for the Firehawk stent at the 4-month follow-up was 64 μm.[14,15] With an expected neointimal thickness of the stent at 3 months of 55 μm for both platforms with a noninferiority margin of 35 μm, a one-sided α level of 0.05, 80% power, and a 3-month attrition rate of 20%, the OCT substudy requires a total of 44 randomized patients (22 in each group). If the conclusion of the noninferiority test is established, we will further carry out superiority testing on the results of the 2 groups. If the *P* value of the test is less than .05, the null hypothesis is rejected, and the conclusion that the test group (Firehawk stent) is superior to the control group (XIENCE stent) is obtained.

Secondary end point analysis

For all secondary end points, the results of the Firehawk and XIENCE EES groups are compared. Clinical end points are assessed during hospital stay at 30 days, 3 months, 6 months, 12 months, 2 years, 3 years, 4 years, and 5 years after the procedure. Angiographic secondary end points are reported at the 12-month follow-up. OCT secondary end points are reported at the 3-month and 12-month follow-up.

Oversight and monitoring

The Steering Committee is formed by principal investigators of the study, representative(s) from the sponsor and the contract research organization. The Steering Committee is responsible for managing the scientific aspects of the study (review and approval of the study design, protocol, study conduct oversight and reporting).

Clinical Events Committee

The Clinical Events Committee (CEC) is an independent committee comprised of 3 interventional cardiologists who are not participants in the study and independent from the sponsor. The CEC is responsible for the categorization of deaths, myocardial infarction, revascularization, and stent thrombosis, based on predefined definitions. Myocardial infarction was defined according to the Third Universal Definition and the other end points according to the Academic Research Consortium (2007).[16,17] All activities are described in a CEC charter, and blinding of source documents is performed as much as possible.

Study monitoring

All centers are qualified before participation. During enrollment and follow-up, monitors will review consistency on the electronic data capture system and source documents during visits to the sites. Monitoring ensures that the trial complies with current Good Clinical Practice, relevant laws and regulations and trial protocol, and finally, obtains secure and accurate data.

Discussion

Revascularization of CTOs with contemporary PCI techniques and devices is endorsed by clinical societies. The 2011 ACC/AHA/SCAI guidelines specify that PCI of a CTO is reasonable when performed by operators with appropriate expertise in patients with appropriate clinical indications and suitable anatomy (Class IIa, level of evidence B).[18] The 2018 ESC guidelines on myocardial revascularization indicate that PCI of a CTO lesion should be considered in patients with angina resistant to medical therapy or with a large area of documented ischemia in the territory of the occluded vessel (Class IIa, level of evidence B).[10] In 2016, the Chinese Society of Cardiology also published the Chinese Percutaneous Coronary Intervention Guidelines, which include a Class IIa recommendation, and upgraded the level of evidence from C to B.[19] However, limited data exist comparing different stent platforms in CTOs. Given the existence of high-performing coronary stents (adequate safety and effectiveness profiles), comparing a novel device with an industry standard such as the XIENCE family stents has been consistently used in recent years.[6,20,21] The all-comers design allows fast enrollment as well as testing the novel device within different lesion types.[22,23] However, subgroup analyses of an all-comers trial, although hypothesis-generating, may require further validation in a dedicated lesion-subtype, well--powered, clinical trial. The TARGET AC trial demonstrated noninferiority of the Firehawk stent when compared to the XIENCE stent and included a modest subgroup of patient with total occlusions; however, CTOs were not prospectively ascertained and there was no stratification for this subtype of lesions, not allowing for definite comparisons in the context of CTOs.[6]

In line with advancements in CTO techniques as well as device iterations,[24] a few studies comparing stent platforms have been completed.[5,15,25] Recently, Qiao et al[4] investigated whether the use of second-generation DES may offer an advantage over first-generation DES in a meta-analysis that included 2 randomized controlled trials and 6 observational studies, amounting to 4583 patients with CTOs treated with DES. The authors showed that the incidences of major adverse cardiac events (odds ratio [OR], 0.68; 95% CI, 0.54-0.85; P =.0008), target vessel revascularization (OR, 0.70; 95% CI, 0.54-0.91; P =.007), and myocardial infarction (OR, 0.58; 95% CI, 0.37-0.93; P =.02) were lower in the second-generation DES than in the first-generation DES. The TARGET CTO trial will compare a sirolimus target-eluting stent with an EES for management of CTOs according to contemporary interventional practices, advancing our knowledge of this important lesion subgroup.

Acknowledgments

The authors extend their heartfelt gratitude to all study participants, hospitals, and researchers contributing to the TARGET CTO trial.

Declaration of competing interest

Dr Ming Zheng and Dr Ruifen Cao are employees of MicroPort. Dr Ernest Spitzer declares institutional contracts with MicroPort Medical, Shanghai, China. Other authors have no relevant disclosures.

Funding sources

The TARGET CTO trial was sponsored by Shanghai MicroPort Medical Co, Ltd, Shanghai, China. The role of the sponsor includes study design, overseeing, logistic support, and review of study reports. Contact: Ming Zheng, MD, at mzheng@microport.com.

Ethics statement

Before the start of the trial, the study director is responsible for submitting the study protocol, informed consent form, and other documents related to the study to the Ethics Committee, and the approval of the Ethics Committee must be obtained before implementation of the clinical trial. After receiving the application, the Ethics Committee should convene a meeting in a timely manner, review the discussion, issue written comments, and attach the list of members who attend the meeting, the specialist, and the signature of the person-in-charge. The sponsor should promptly report the serious adverse events occurring during the study, including the risks and other problems of the patients. Any changes to the study protocol must first be approved by the Ethics Committee and filed with the Ethics Committee.

Subjects who meet the clinical eligibility will be required to sign the study's informed consent form approved by the Ethics Committee before any study-specific tests or procedures are performed.

Supplementary material

To access the supplementary material accompanying this article, visit the online version of the *Journal of the Society for Cardiovascular Angiography & Interventions* at 10.1016/j.jscai.2022.100511.

References

1. Stone GW, Kandzari DE, Mehran R, et al. Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: part I. *Circulation*. 2005;112(15):2364–2372.
2. Ybarra LF, Rinfret S, Brilakis ES, et al. Definitions and clinical trial design principles for coronary artery chronic total occlusion therapies: CTO-ARC consensus recommendations. *Circulation*. 2021;143(5):479–500.
3. van Veelen A, Elias J, van Dongen IM, Hoebers LPC, Claessen BEPM, Henriques JPS. Percutaneous coronary intervention versus medical therapy for chronic total coronary occlusions: a systematic review and meta-analysis of randomised trials. *Neth Heart J*. 2021;29(1):30–41.
4. Qiao X, Zhang WJ, Guo WF, Li Y, Liang XY, Wang ZL. Comparison of clinical outcomes between second-and first-generation drug-eluting stents in patients with chronic total occlusion lesion: a meta-analysis. *Front Cardiovasc Med*. 2021;8:598046.
5. Teeuwen K, van der Schaaf RJ, Adriaenssens T, et al. Randomized multicenter trial investigating angiographic outcomes of hybrid sirolimus-eluting stents with biodegradable polymer compared with everolimus-eluting stents with durable

polymer in chronic total occlusions: the PRISON IV trial. *JACC Cardiovasc Interv*. 2017;10(2):133–143.
6. Xu B, Saito Y, Baumbach A, et al. 2-year clinical outcomes of an abluminal groove-filled biodegradable-polymer sirolimus-eluting stent compared with a durable-polymer everolimus-eluting stent. *JACC Cardiovasc Interv*. 2019;12(17):1679–1687.
7. King 3rd SB, Smith Jr SC, Hirshfeld Jr JW, et al. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2007 writing group to review new evidence and update the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention, writing on behalf of the 2005 Writing Committee. *Circulation*. 2008;117(2):261–295.
8. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2016;68(10):1082–1115.
9. Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC), the European Association for Cardio-Thoracic Surgery (EACTS), European Association for Percutaneous Cardiovascular Interventions (EAPCI), et al. Guidelines on myocardial revascularization. *Eur Heart J*. 2010;31(20):2501–2555.
10. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40(2):87–165.
11. Serruys PW, Ong AT, Piek JJ, et al. A randomized comparison of a durable polymer everolimus-eluting stent with a bare metal coronary stent: the SPIRIT first trial. *EuroIntervention*. 2005;1(1):58–65.
12. Serruys PW, Ruygrok P, Neuzner J, et al. A randomised comparison of an everolimus-eluting coronary stent with a paclitaxel-eluting coronary stent: the SPIRIT II trial. *EuroIntervention*. 2006;2(3):286–294.
13. Gao RL, Xu B, Lansky AJ, et al. A randomised comparison of a novel abluminal groove-filled biodegradable polymer sirolimus-eluting stent with a durable polymer everolimus-eluting stent: clinical and angiographic follow-up of the TARGET I trial. *EuroIntervention*. 2013;9(1):75–83.
14. Qian J, Xu B, Lansky AJ, et al. First report of a novel abluminal groove filled biodegradable polymer rapamycin-eluting stent in de novo coronary artery disease: results of the first in man FIREHAWK trial. *Chin Med J (Engl)*. 2012;125(6):970–976.
15. Moreno R, Garcia E, Teles R, et al. Randomized comparison of sirolimus-eluting and everolimus-eluting coronary stents in the treatment of total coronary occlusions: results from the chronic coronary occlusion treated by everolimus-eluting stent randomized trial. *Circ Cardiovasc Interv*. 2013;6(1):21–28.
16. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115(17):2344–2351.
17. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Circulation*. 2012;126(16):2020–2035.
18. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation*. 2011;124(23):e574–e651.
19. Section of Interventional Cardiology of Chinese Society of Cardiology of Chinese Medical Association, Specialty Committee on Prevention and Treatment of Thrombosis of Chinese College of Cardiovascular Physicians, Editorial Board of Chinese Journal of Cardiology. Chinese guideline for percutaneous coronary intervention (2016). Article in Chinese *Zhonghua Xin Xue Guan Bing Za Zhi*. 2016;44(5):382–400.
20. de Winter RJ, Zaman A, Hara H, et al. Sirolimus-eluting stents with ultrathin struts versus everolimus-eluting stents for patients undergoing percutaneous coronary intervention: final three-year results of the TALENT trial. *EuroIntervention*. 2022;18(6):492–502.
21. Takahashi K, Serruys PW, Kogame N, et al. Final 3-year outcomes of MiStent biodegradable polymer crystalline sirolimus-eluting stent versus XIENCE permanent polymer everolimus-eluting stent: insights from the DESSOLVE III all-comers randomized trial. *Circ Cardiovasc Interv*. 2020;13(6):e008737.
22. de Boer SP, Lenzen MJ, Oemrawsingh RM, et al. Evaluating the "all-comers" design: a comparison of participants in two "all-comers" PCI trials with non-participants. *Eur Heart J*. 2011;32(17):2161–2167.
23. Gragnano F, Zwahlen M, Vranckx P, et al. Ticagrelor monotherapy or dual antiplatelet therapy after drug-eluting stent implantation: per-protocol analysis of the GLOBAL LEADERS trial. *J Am Heart Assoc*. 2022;11(10), e024291.
24. Brilakis ES, Mashayekhi K, Tsuchikane E, et al. Guiding principles for chronic total occlusion percutaneous coronary intervention. *Circulation*. 2019;140(5):420–433.
25. Teeuwen K, Van den Branden BJ, Koolen JJ, et al. Three-year clinical outcome in the Primary Stenting of Totally Occluded Native Coronary Arteries III (PRISON III) trial: a randomised comparison between sirolimus-eluting stent implantation and zotarolimus-eluting stent implantation for the treatment of total coronary occlusions. *EuroIntervention*. 2015;10(11):1272–1275.