Randomized Multi-center Trial Investigating the Angiographic Outcome of Hybrid Sirolimus-eluting Stents with Biodegradable Polymer Against Everolimus-eluting Stents with Durable Polymer in Chronic Total Occlusions (PRISON IV)

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Running title: Hybrid Sirolimus Versus Everolimus Stents in CTO

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ABSTRACT

Background: The introduction of drug-eluting stents (DES) revolutionized the treatment of chronic total occlusions (CTO). However, limited data is available of new-generation DES with biodegradable polymers in CTOs.

Objectives: This study investigated the efficacy and safety of the hybrid ultra-thin strut sirolimus-eluting stent (SES) with biodegradable polymers against the thin strut everolimus-eluting stent (EES) with durable polymers in successfully recanalized CTOs.

Methods: This multi-center trial randomized patients, after successful CTO recanalization, to either SES or EES. The primary non-inferiority end point was in-segment late lumen loss (non-inferiority margin of 0.2mm). Secondary end points included in-stent late lumen loss and clinical end points.

Results: Overall, 330 patients were included. At 9 months, angiography was available in 281/330 (85%) patients. Duration of occlusion ≥3 months was 92.5% with mean stent length of 52.4±28.1 mm vs. 52.3±26.5 mm in the SES and EES group. The primary non-inferiority end point in-segment late lumen loss was not met for SES against EES (0.13±0.63 mm versus 0.02±0.47 mm; p=0.08, 2-sided; difference=0.11 mm; 95% confidence interval, -0.01 to 0.25; $p_{non\text{-}inferiority}$=0.11, 1-sided). In-stent late lumen loss was comparable between SES and EES (0.12±0.59 versus 0.07±0.46 mm; p=0.52). The incidence of in-stent/in-segment binary restenosis was significantly higher with SES against EES (8.0% versus 2.1%; p=0.028) with comparable rates of reocclusions (2.2% versus 1.4%; p = 0.68). Clinically indicated target lesion –and vessel revascularization (9.2% versus 4.0%; p=0.08 and 9.2% versus 6.0%; p=0.33), target vessel failure (9.9% versus 6.6%; p=0.35) and definite or probable stent thrombosis (0.7% versus 0.7%; p=1.0) were comparable in the SES and EES group.

Conclusions: This randomized trial failed to show non-inferiority of hybrid SES relative to EES in terms of in-segment late lumen loss in successfully recanalized chronic total occlusions. Furthermore, we found a statistically significantly higher rate of binary restenosis with SES.

KEY WORDS: Chronic total occlusion, Drug-eluting stent, Percutaneous Coronary Intervention, Biodegradable polymer

CONDENSED ABSTRACT

This prospective randomized, multi-center (PRISON IV) trial investigated the angiographic outcome of hybrid sirolimus-eluting stent with biodegradable polymer (SES) against the everolimus-eluting stent with durable polymer (EES) in patients with successfully recanalized chronic total occlusions (CTO). At 9-months, the primary non-inferiority end point of in-segment late luminal loss was not met for SES against EES (0.13±0.63 mm versus 0.02±0.47 mm; p=0.08, 2-sided; difference=0.11 mm; 95% confidence interval, -0.01 to 0.25; pnon-inferiority=0.11, 1-sided). We found a statistically significantly higher rate of in-segment/in-stent binary restenosis (8.0% versus 2.1%; p=0.028) with SES. Future stent developments should focus on the challenging characteristics of CTOs.

ABBREVIATIONS

CCS	Canadian Cardiovascular Society Grading of Angina Score
CTO	chronic total occlusion
EES	everolimus-eluting stent
MACE	major adverse cardiac events
MLD	minimal lumen diameter
SES	hybrid sirolimus-eluting stent
TCO	total coronary occlusion

TIMI	Thrombolysis In Myocardial Infarction
TLR	target lesion revascularization
TVF	target vessel failure
TVR	target vessel revascularization.

INTRODUCTION

The field of percutaneous coronary intervention for chronic total occlusions (CTO) experienced a paradigm shift after the introduction of drug-eluting stents (DES). More than a decade ago PCI for CTO was hampered by high rates of restenosis and reocclusions with bare metal stents (BMS) and balloon angioplasty.(1) The introduction of DES demonstrated important reduction in target vessel revascularizations against BMS.(2,3) Together with sophisticated innovations like the retrograde approach, antegrade dissection re-entry and hybrid algorithm, percutaneous CTO recanalizations have become an important alternative to surgical revascularization.(4) Despite improving results with first-generation DES concerns were raised after observing increased rates of very late stent thrombosis (VLST).(5) Second-generation DES, with thin-strut design and different anti-proliferative drugs, showed comparable angiographic and clinical outcome compared to first generation DES in CTO.(6,7) Chronic inflammation, hypersensitivity reactions on durable polymers and late acquired stent strut malapposition were suggested as possible mechanisms of very late target vessel failure.(8,9) The novel 'Orsiro' hybrid ultra-thin strut sirolimus-eluting stent platform with biodegradable polymer (SES; Orsiro, Biotronik, Berlin, Germany) was designed to overcome potential drawbacks of earlier generation drugs-eluting stents. The cobalt-chronium stent consist of ultra-thin struts (60 μm) covered with silicon carbide layer to reduce passive ion release. The stent is coated with anti-proliferative sirolimus drug embedded in biodegradable poly-L lactic acid polymer (PLLA), which gradually degrades in 12 to 24 months. In the BIOFLOW II study SES demonstrated comparable angiographic results to thin-strut (81 μm) everolimus-eluting stents with durable polymers (EES; Xience, Abbott Vascular, Santa Clara, CA, USA) in de novo lesions.(10)

In this prospective, multi-center, single-blinded trial we investigated the angiographic

outcome of the new hybrid sirolimus-eluting stent with biodegradable polymer against the everolimus-eluting stent with durable polymer in chronic total occlusions.

METHODS

Study oversight

This investigator initiated, prospective, randomized, single blinded, multi-center clinical trial was performed in two Belgian and six Dutch high-volume PCI centers. The Research and Development Department at the St. Antonius Hospital Nieuwegein was responsible for data collection and monitoring. Independent study monitors verified all source data on site. Data and Safety Monitoring Board reviewed all cardiac and noncardiac adverse events. Two external experts not involved in the study adjudicated all clinical end points in a blinded fashion. The study authors vouch for the accuracy and completeness of the data and the analyses. The study was supported by unrestricted grants from Biotronik SE & Co. KG, Berlin, Germany and Abbott Vascular, Santa Clara, CA, USA. The sponsors were not involved in the study design, data collection and/or analysis, drafting the manuscript or the decision to submit the manuscript. All institutional review boards of the local centers approved the study. Written informed consent was obtained prior to the procedure. The study was performed in compliance with the standards of Good Clinical Practice (ICH/E6/R1) and the Declaration of Helsinki (Washington 2002). This trial is registered with ClinicalTrials.gov NCT01516723. The rationale and design of this study was published previously.(12)

Recruitment, enrollment and randomization

Between February 2012 and June 2015 a total of 330 consecutive patients with successfully recanalized native total or chronic total coronary occlusions were randomized to the hybrid sirolimus-eluting stent (Orsiro, Biotronik, Berlin, Germany) or the everolimus-eluting stent

(Xience Prime/Xpedition; Abbott Vascular, Santa Clara, CA, USA). The rationale and design of the study was explained in detail previously.(12) Patients older than 18 years were eligible for study participation, if presenting with total or chronic total occlusions with an estimated duration of ≥ 4 weeks; evidence of ischemia and viability in the territory of the occlusion; reference diameter of the target vessel was between 2.25 and 4.0 mm. The most important exclusion criteria were total occlusions of venous or arterial bypass grafts or in-stent occlusions. The randomization procedure was initiated after successful wire passage with successful predilatation of the lesion. Randomization was performed using an interactive Web-based randomization system. Patients and referring physicians were blinded to the assigned treatment group.

Definitions

Total coronary occlusion (TCO) was defined as absence of antegrade flow of contrast distal to the occlusion (Thrombolysis In Myocardial Infarction [TIMI] flow 0 according to the Thrombolysis In Myocardial Infarction Grade flow) or minimal antegrade flow of contrast distal to the occlusion TIMI 1 flow in the presence of bridging collaterals. The duration of the occlusion was estimated to be ≥ 4 weeks based on clinical and/or angiographic information. Chronic total occlusion (CTO) was defined as TCO with an estimated duration of ≥ 3 months. Procedural success was defined as < 30% residual stenosis on visual assessment and TIMI flow III.

Procedure

The procedure was performed by single or double access site from the femoral and/or radial artery with standard coronary catherization techniques. All patients received dual anti-platelet therapy prior to the procedure, or triple therapy in case of indication for oral anti-coagulation for at least 12 months according to guidelines of the European Society of Cardiology for stable

coronary disease or acute coronary syndromes. An angiographic follow-up was mandated at 9 months. Operators were instructed to use fractional flow reserve if they observed intermediate target vessel stenosis < 70% with or without angina or > 70% in the absence of angina, during follow-up angiography.

Quantitative coronary analysis

All coronary angiograms were assessed offline by an independent angiographic core laboratory (St Antonius Hospital Angiographic Core Laboratory, Nieuwegein, the Netherlands) with automatic edge-detection software (CMS version 5.3; Medis Medical Imaging Systems, Leiden, the Netherlands) by experienced personnel blinded for clinical information and allocated stent. The occlusion length was measured with bilateral contrast injections or after predilatation in case of unilateral contrast injection. CTO complexity was evaluated with J-CTO score and angiographic classification of in-stent restenosis was used to classify all binary restenosis.(13,14) Quantitative measurements included the diameter of the reference vessel, the minimal lumen diameter (MLD), percentage of diameter stenosis (difference between reference vessel diameter and MLD/ reference diameter x 100), and late lumen loss (difference between MLD after the procedure and MLD at follow-up). Quantitative analysis was performed in the proximal -and distal 5 mm segment, stent edges, in-stent and in-segment (defined as the stented segment including margins of 5 mm proximal and distal), after predilatation, post-procedural and at 9-month follow-up. Binary in-stent restenosis was defined as ≥ 50% diameter stenosis within the stent. In-segment binary restenosis was defined as ≥ 50% diameter stenosis located in the stent and/or at the 5 mm proximal or 5 mm distal edge. Reocclusion was defined as recurrent total occlusion at the previous angioplasty site.

Clinical follow-up

An independent clinical event committee adjudicated all clinical end points. Clinical follow-up was obtained during hospital stay and at 1, 6, 9 and 12 months. The vital status of patients was checked in the national population registry (Dutch Central Bureau of Statistics), if they were lost to follow-up or withdrew informed consent. Percutaneous or surgical revascularization were clinically driven if stenosis of the treated lesion was ≥ 50% of the lumen diameter on the basis of quantitative coronary angiography in the presence of ischemic signs and/or symptoms, or if there is diameter stenosis ≥ 70% irrespective of the presence or absence of ischemic signs or symptoms. Death, myocardial infarction (MI; defined as the presence of new significant Q waves or an elevation of creatine kinase or its MB isoenzyme to at least twice the upper reference limit) and clinically driven target lesion revascularization (TLR; defined as revascularization due to a stenosis within a 5 mm border proximal or distal to the stent) were recorded as major adverse cardiac events (MACE). Other secondary clinical end points included clinically driven target vessel revascularization (TVR; defined as revascularization in the entire coronary vessel proximal and distal of the target lesion, including revascularization in side branches), target vessel failure (TVF; a composite of cardiac death, MI and clinically driven TVR) and stent thrombosis. Finally, the occurrence of angina was recorded with the Canadian Cardiovascular Society Grading of Angina Score (CCS).

End points

The primary non-inferiority end point was in-segment late lumen loss at 9-month angiography assessed with quantitative coronary analysis. Secondary angiographic end points included; in-stent late lumen loss, MLD, in-stent and in-segment percentage of diameter stenosis, binary restenosis and reocclusions at 9 months. Secondary individual and composite clinical end points were clinically indicated TLR/ TVR, MI, Death (Cardiac and non-cardiac), ST, TVF and MACE.

Statistics

In the study design, we hypothesized that the angiographic outcome of the hybrid sirolimus-eluting stent was non-inferior to the everolimus-eluting stent in successfully recanalized TCO/CTOs. The non-inferiority margin was set at a conventional level of 0.2 mm. The expected late lumen loss was 0.16 mm for both groups with a standard deviation of 0.55 mm.(15,16) The null hypothesis would be rejected if the upper boundary of the 95% confidence interval of the observed difference in in-segment late lumen loss exceeded the non-inferiority margin. The power of the study was > 85% with α level of 5% and 140 patients per group. A total of 165 patients per group were randomized to account for 20% loss in follow-up angiograms. The primary and secondary end points were analyzed by intention to treat. The Westlake-Schuirmann test (1-sided) was used for the primary non-inferiority end point. For other secondary clinical and angiographic end points, the 2-sample *t* test (2-sided) was used to compare continuous variables and fisher's test to compare binary and categorical outcomes. Cumulative incidence of clinical events was analyzed using the Kaplan-Meier method and compared between treatment groups with log-rank test. All analyses were performed using R (version 3.3, www.r-project.org).

RESULTS

Enrollment and randomization

An estimated 713 subjects were screened resulting in 330 randomized patients equally divided between the everolimus-eluting and hybrid sirolimus-eluting stent group (Figure 1). Objection for follow-up angiography (22.7%) and failure of wire crossing during the recanalization attempt (30.7%) were main reasons for screening and enrollment exclusion. Three fault inclusions were observed in the EES group after randomization. Two subjects were randomized with in-stent CTO. One patient was incorrectly randomized after successful reopening of the proximal CTO

and failure of recanalizing the distal occlusion in a misjudged tandem CTO in the target vessel. Notwithstanding, all subjects were included in the intention to treat analysis.

Baseline clinical, procedural characteristics and outcome

Baseline clinical and procedural characteristics were evenly distributed between both groups except for mean J-CTO score 1.8 ± 1.1 and 2.0 ± 1.1 p = 0.03 with SES against EES. Results are shown in Tables 1 and 2. The mean age of the participants was 62-years old with estimated duration of occlusion ≥ 3 months (CTO) 89.2% with SES vs. 95.2% with EES (p = 0.09) and mean occlusion length of 20.4 ± 12.4 with SES vs. 20.9 ± 14.5 mm with EES (p = 0.74) with SES and EES. The majority of procedures were performed from single catheter access (70%) from either radial or femoral artery. Dual catheter assess (30%) with retrograde approach as primary strategy was performed in 14% of all cases. The average number of implanted stents was 2.1 ± 1.06 vs. 2.0 ± 0.96 with mean total stent length of 52.3 ± 26.6 vs. 52.4 ± 28.1 mm for SES and EES. Periprocedural complications are demonstrated in Table 3. Two patients needed rescue pericardiocentesis in the SES group. Donor artery dissection, caused by the contralateral catheter in retrograde procedures requiring PCI, was observed in one patient in each treatment arm. Untreated dissections in the distal coronary bed of the target vessel occurred in five subjects evenly distributed between both groups. Post-procedural success was 98.8% in both groups. TIMI flow 0 was observed after failed recanalization in the EES group. One case in each group showed TIMI II flow caused by untreated dissections in the distal coronary bed without repeated revascularization at follow-up. One case demonstrated TIMI II flow with SES after using the limited antegrade dissection re-entry technique (ADRT) requiring clinical target lesion revascularization during follow-up. Other patients treated with ADRT were free of repeated revascularizations during follow-up.

Angiographic outcome

All angiographic end points are shown in Table 4 and Figure 2. At 9 months, follow-up angiography was available in 281/330 (85%) patients. There were no significant differences in baseline characteristics between patient with and without angiographic follow-up at 9-month (Appendix A). In-segment late lumen loss was 0.13 ± 0.63 mm in the SES group against 0.02 ± 0.47 mm in the EES group (p = 0.08, 2-sided). The observed difference in in-segment late lumen loss was 0.11 mm with 95% confidence interval of -0.01 to 0.25. The upper limit of the 95% confidence interval exceeded the non-inferiority margin of 0.20 mm. Consequently; the powered non-inferiority end point was not met for hybrid sirolimus-eluting stents against everolimus-eluting stents ($p_{non\text{-}inferiority}$ = 0.11, 1-sided). Post-hoc analysis demonstrated non-inferiority of the secondary end point in-stent late lumen loss (0.12 ± 0.59 vs. 0.07 ± 0.46 mm, p = 0.52, 2-sided; confidence interval, -0.08 to 0.16, $p_{non\text{-}inferiority}$ = 0.006, 1-sided) with SES and EES, if the non-inferiority assumptions of the primary end point were applied. The secondary angiographic end points in-stent late lumen loss, in-stent/segment MLD and in-stent/segment diameter stenosis were comparable between SES and EES. The rates of in-stent/in-segment binary restenosis were significantly higher with SES against EES 8.0% vs. 2.1% (p = 0.028) with comparable rate of reocclusions 1.4% vs. 2.2% (p = 0.68). All non-occlusive binary restenosis were classified as focal (type Ic).(13) The occurrence of binary restenosis on the previously occluded site was 4.4% vs. 2.1% (p = 0.50) with SES and EES. Post-hoc sensitivity analysis (Appendix B) of baseline characteristics occlusion duration > 3 months, symptomatic CCS score ≥ 3 at baseline, post-dilatation and dichotomous stent length ≤ 30 mm or > 30 mm demonstrated no interaction with the primary end point in-segment late lumen loss between the treatment groups.

Clinical follow-up

Clinical follow-up at 12 months was available in 99% of all subjects (Figure 1). Two subjects were lost to follow-up and one subject withdrew consent. Of those, two subjects were alive at 12 months, confirmed in the national population registry, and one subject remained lost to follow-up beyond 9 months due to emigration. All results on Angina Grading by CCS score at baseline and 12 months; individual and composite clinical events at 12 months are shown in Table 5. Clinically indicated target lesion -and vessel revascularization, target vessel failure and MACE were comparable between both groups. Two subjects in the SES group received non-clinical TLR with balloon angioplasty after observing severe stent strut malapposition with optical coherence tomography at 9 months. There was only one probable or definite stent thrombosis in each stent group (0.7% vs. 0.7%; $p = 1.0$). Angina graded by CCS score was significantly reduced in each treatment arm from index procedure to 12-month follow-up (both $p < 0.001$) with no difference between both groups. ($p = 0.77$ and $p = 0.60$).

DISCUSSION

This randomized, prospective, multi-center, single blinded study investigated the angiographic and clinical outcomes of hybrid ultra-thin strut sirolimus-eluting stents with biodegradable polymer against thin-strut everolimus-eluting stents with durable polymer in chronic total occlusions. The major findings were; the non-inferiority end point of in-segment late lumen loss was not met for SES against EES, the rate of binary restenosis was significantly higher with SES versus EES, and clinical end points and angina relief were comparable between both groups.

The novel design of the hybrid sirolimus-eluting stent with ultra-thin struts, silicon diffusion barrier and biodegradable polymer, seems attractive to promote arterial healing, reduce inflammation, and overcome potential risks of hypersensitivity reactions to permanent polymers. Ex vivo flow studies showed strong correlations of reduced thrombogenicity by decreasing strut

thickness and application of polymer/drug coatings on bare metal stents.(17) Together with biodegradable PLLA, which demonstrated reduced inflammation scores and neointimal growth compared to permanent polymers, the improved design of SES seems the next logical step to reduce restenosis and stent thrombosis in chronic total occlusions.(18) We chose the most reputable stent device, the everolimus-eluting stent (EES; Xience), as comparator to challenge the novel 'Orsiro' stent device in this complex lesion subset. The EES showed robust evidence of efficacy and safety compared to first generation drug-eluting stents in all type of coronary lesions, including chronic total occlusions.(7,19-21)

Our findings are not in line to earlier presented results from the BIOFLOW-II study. In this study, angiographic non-inferiority was demonstrated between SES and EES in simple de novo lesions with no difference of in-stent –or segment late lumen loss (0.10 ± 0.32 vs. 0.11 ± 0.29 mm; p = 0.98, $P_{\text{noninferiority}} < 0.0001$ and 0.09 ± 0.35 vs. 0.09 ± 0.33 mm; p = 0.86). Angiographic late lumen loss is a powerful predictor for present or future binary restenosis or clinical revascularizations, and particularly useful in 'smaller' trials not powered to assess clinical end points.(22) Our results showed that, the predetermined primary end point in-segment late lumen loss was not met for SES against EES. This was mainly caused by an increased rate of focal in-stent restenosis in the SES group. Obviously, both trials consist of patients with complete different lesion complexity. In comparison to simple de novo lesions, chronic total occlusions are more commonly much longer and severely calcified lesions, which necessitate stents with high radial strength to maintain acute -and late vessel recoil after PCI. Secondly, recanalized CTOs require frequently multiple overlapping stents in adjacent segments. Thirdly, reopened CTOs are subjected to flow dependent vessel remodeling and late vasodilation, which may lead to late acquired stent strut malapposition, highlighting the unique challenges related

with stent implantation in CTOs.(23)

The rate of 9-month binary in-stent restenosis was higher in SES compared to EES. All non-occlusive binary restenosis were focal in-stent (SES vs. EES; 5.8% vs. 0.7%, p = 0.032). Interestingly, all restenosis with EES occurred at the previous occlusion site in contrast to SES demonstrating restenosis in both the previously occluded and non-occlusive segments. The mechanism behind the focal restenosis remains speculative, however it should be further evaluated if the 25% reduction in strut thickness in SES up to 3.0 mm diameter might compromise the radial strength needed in these selected complex coronary lesions (CTOs).

At 12 months, clinical events were comparable between both stent groups. Though, this study was not powered for clinical end points, the low rate of stent thrombosis in both stent groups was reassuring. The LEADERS trial demonstrated a proof of concept with biodegradable polymer stent technology, by showing landmark reduction in very late stent thrombosis with associated events at 5-year, with thick-strut (120 μm) biolimus-eluting stent with biodegradable polymers (BioMatrix Flex, Biosensors Inc., Newport Beach, California) compared to thick-strut (140 μm) first generation sirolimus-eluting DES with durable polymer (Cypher SELECT, Cordis, Miami Lakes, Florida).(24) In contrast, the Danish all-comer trial, SORT OUT VII, prospectively investigated ultra-thin strut SES against thick-strut (120 μm) biolimus-eluting stent (Nobori, Terumo, Tokyo, Japan) both with biodegradable polymers. (28) At 1-year target-lesion failure was non-inferior, (3.8% vs. 4.6%; $p_{\text{non-inferiority}} < 0.0001$) with significantly lower rate of subacute stent thrombosis (0.1% vs. 0.6%; p = 0.05) in the SES group. Moreover, Han et al., showed no difference in stent thrombosis and clinical outcome, between two similar thin-strut stent devices (80 μm cobalt-chronium) comparing durable against biodegradable polymer coatings. These findings confirm the importance of stent design and strut thickness on clinical

outcome.(26)

Both stent devices used in this trial were investigated earlier in all-comer patients in the BIOSCIENCE trial.(27) At 12 months, the primary end point of target vessel failure with SES was non-inferior to EES. Our results demonstrated higher rates of clinically indicated target lesion revascularization, especially with SES compared to the BIOSCIENCE trial. (9.2% vs. 4%, p = 0.084; BIOSCIENCE 3.4% vs. 2.4%, p = 0.27 with SES and EES). This could be partially caused by routine angiographic follow-up and the difference in lesion complexity, however these findings merit longer-term clinical follow-up.

Quality of life was measured using the CCS score demonstrating significant angina reduction after the index procedure with either study stent with no difference between both stent groups. Successful recanalization of chronic total occlusions reduces ischemic burden, favors left ventricular function and relieves angina in symptomatic patients.(29) Quality of health is gaining importance in interventional cardiology next to sole reduction of clinical events. In this study, angina was registered with an easy acquirable CCS score, which has shown reasonable correlation with the more sophisticated 7-domain Seattle Angina Questionnaire in stable coronary artery disease.(30)

LIMITATIONS

There are limitations to acknowledge. Our definition of TCO and inclusion criterion for study participation was different from the accepted CTO definition. Nevertheless, more than 92% of the included patients satisfied the accepted CTO definition of estimated duration equal or more than 3 months with TIMI flow 0. This study represented a population of ‘Real-World’ CTO practice.(31) However, the results should be cautiously extrapolated to CTO patients, presenting with higher prevalence of co-morbidities and more complex lesions characteristics, requiring

higher rate of advanced recanalization techniques embraced in the state-of-the art-hybrid algorithm. Furthermore, there was a difference in CTO complexity expressed by the J-CTO score between both groups. Though, bias of the overall angiographic and clinical results seems unlikely with lower J-CTO score in the SES group. Despite operators were instructed to perform high pressure post-dilatation, the reported rate of post-dilatations was low (35%). On the other hand, the average maximal balloon or stent pressure was well above the nominal stent pressure (16.8 ± 4.0 vs. 16.6 ± 3.7 atmosphere with SES and EES) and sensitivity analysis demonstrated no interaction between post-dilatation and in-segment late lumen loss p-for-interaction = 0.97. Data on procedural metrics, contrast use, radiation and fluoroscopy time were not complete and should be interpreted cautiously. Undetected binary restenosis or reocclusions cannot be excluded, in spite a reasonable rate of angiographic follow-up (>85%). Additionally, 20% loss of follow-up angiography was anticipated in the predefined power calculation for the primary end point. Furthermore, this study was susceptible to non-clinically indicated revascularizations with planned repeated angiography on 9 months. To minimize these revascularizations, all participating centers were instructed during study initiation, to use additional fractional flow reserve in all observed intermediate lesions. Finally, this study was not powered for clinical end points and therefore these should be interpreted only as hypothesis generating.

CONCLUSION

This prospective, multi-center randomized trial failed to show non-inferiority of hybrid ultra-thin strut sirolimus-eluting stent with biodegradable polymer relative to thin-strut everolimus-eluting stent with durable polymer in terms of in-segment late lumen loss in successfully recanalized chronic total occlusions. Furthermore, the rate of binary restenosis was statistically significantly higher with SES.

PERSPECTIVES

WHAT IS KNOWN?

The introduction of drug-eluting stents revolutionized treatment efficacy of percutaneous coronary intervention for chronic total occlusions. Novel stent devices with biodegradable polymer were designed after observing an increased rate of very late stent thrombosis with DES.

WHAT IS NEW?

At 9 months, the novel ultra-thin strut sirolimus-eluting stent with biodegradable polymer did not improve angiographic outcome compared to thin-strut everolimus-eluting stent with durable polymer in patients with successfully recanalized chronic total occlusions.

WHAT IS NEXT?

Future developments in stent technology should focus on the challenging characteristics of chronic total occlusions to improve device efficacy and clinical outcome.

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FIGURE LEGEND

Figure 1. Enrollment and Randomization

*The total of screening failures and excluded were estimated on adequate registration at one center [screening failures/excluded registered at the center dived by number of randomized subjects (87) multiplied by 330); § with available 9-month angiographic follow-up; ‡ without angiographic follow-up; ITT, intention to treat.

Figure 2. In-segment Late Lumen Loss

The mean difference in late lumen loss for primary end point in-segment late lumen loss and post-hoc analysis of in-stent late lumen loss assessed for non-inferiority (A), Cumulative frequency (%) of in-segment late lumen loss (B), Binary in-segment restenosis (%) at 9-month follow-up angiography (C), Cumulative frequency (%) of in-stent late lumen loss (D) between SES and EES in patients with successfully recanalized chronic total occlusions.

Table 1. Baseline clinical characteristics

		Hybrid Sirolimus (SES) n=165	Everolimus (EES) n=165	p-value
Age (yr), mean ± standard deviation		62.4 ± 10.5	62.8 ± 9.5	0.73
Male sex (%)		122 (73.9)	137 (83.0)	0.06
Estimated occlusion duration > 3 months (%)		157 (95.2)	148 (89.7)	0.09
Initial presentation (%)				0.99
	Stable AP	115 (69.7)	115 (69.7)	
	Unstable AP	10 (6.1)	12 (7.3)	
	ACS*	18 (10.9)	17 (10.3)	
	Coincidental finding	6 (3.6)	5 (3.0)	
	Unclassified	16 (9.7)	16 (9.7)	
Non-invasive ischemia detection (%)				
	Bicycle test	45 (27.3)	42 (25.5)	0.80
	Nuclear imaging	44 (26.7)	45 (27.3)	0.99
	MRI	10 (6.1)	13 (7.9)	0.67
	Coronary CT	6 (3.6)	7 (4.2)	0.99
	Not performed/unknown	64 (38.8)	74 (44.8)	0.32

CCS angina class (%)				0.77
	No AP	22 (13.3)	14 (8.5)	
	I	3 (1.8)	12 (7.3)	
	II	95 (57.6)	97 (58.8)	
	III	37 (22.4)	33 (20.0)	
	IV	8 (4.8)	9 (5.5)	
LVEF (%)				0.46
	>50%	144 (87.3)	139 (84.2)	
	30-50%	17 (10.3)	21 (12.7)	
	<30%	4 (2.4)	5 (3.0)	
Risk factors (%)				
	Smoking			0.28
	Never	63 (38.2)	50 (30.3)	
	Stopped >6 weeks	53 (32.1)	56 (33.9)	
	Current**	49 (29.7)	59 (35.8)	
	Diabetes Mellitus	31 (18.8)	34 (20.6)	0.78
	Non-insulin requiring	18 (10.9)	24 (14.5)	0.31
	Insulin requiring	13 (7.9)	10 (6.1)	
	Hyperlipidaemia	161 (97.6)	155 (93.9)	0.17

History of (%)	Hypertension		148 (89.7)	154 (93.3)	0.24
	Familial risk		79 (47.9)	87 (52.7)	0.32
	Renal condition (GFR)				0.54
		Normal (>60)	150 (90.9)	148 (89.7)	
		Mildly decreased. (45-59)	12 (7.3)	12 (7.3)	
		Moderate decreased (30-44)	2 (1.2)	3 (1.8)	
		Severely decreased (<30)	1 (0.6)	2 (1.2)	
	Previous MI (%)		52 (31.5)	48 (29.1)	0.81
	Previous intervention (%)	PCI	47 (28.5)	50 (30.3)	0.81
		CABG	6 (3.6)	11 (6.7)	0.32
	Previous attempts at TLR (%)		21 (12.7)	23 (13.9)	0.87
	Previous stroke (%)		13 (7.9)	11 (6.7)	0.83

Values are mean ± standard deviation and counts (%); *only troponine and no creatine kinase or mb iso-enzym above the upper 99% reference limit; ** Including stopped <6 weeks; ACS, Acute coronary syndrome; AP, angina pectoris; CABG, Coronary artery bypass graft; CT, computer tomography; EES, everolimus-eluting stent; GFR, glomerular filtration ratio; MI, myocardial infarction; MRI, magnetic resonance imaging; PCI, percutaneous coronary intervention; SES, hybrid sirolimus-eluting stents; TLR, target lesion revascularization.

Table 2. Baseline procedural characteristics

		Hybrid Sirolimus (SES) n=165	Everolimus (EES) n=165	p-value
Coronary artery disease (%)				0.90
	1 vessel	105 (64.5)	108 (65.5)	
	2 vessel	50 (30.3)	46 (27.9)	
	3 vessel	10 (6.1)	11 (6.7)	
Occluded vessel (%)				0.68
	RCA	94 (57.0)	87 (52.7)	
	LAD	48 (29.1)	50 (30.3)	
	RCX	23 (13.9)	28 (17.0)	
Collateral filling (%)		156 (94.5)	159 (96.4)	0.60
	Bridge collaterals	73 (44.2)	70 (42.4)	0.82
	Retrograde filling	151 (91.5)	152 (92.1)	0.99
TIMI flow pre procedure (%)				0.29
	0	150 (90.9)	156 (94.5)	
	I	15 (9.1)	9 (5.5)	
	II	0 (0.0)	0 (0.0)	
	III	0 (0.0)	0 (0.0)	

		Hybrid Sirolimus (Orsiro), n=165	Everolimus (Xience), n=165	p-value
Antiplatelet therapy (%)*				0.78
	Clopidogrel	105 (65.6)	103 (62.8)	
	Prasugrel	34 (21.3)	35 (21.3)	
	Ticagrelor	21 (13.3)	26 (15.9)	
Catheter size (%)				0.59
	5 French	1 (0.6)	4 (2.4)	
	6 French	133 (81.1)	128 (77.6)	
	7 French	23 (14.0)	24 (14.5)	
	8 French	7 (4.3)	9 (5.5)	
Sheath location (%)				0.72
Single catheter access				
	Femoral	63 (38.2)	65 (39.4)	
	Radial	51 (30.9)	51 (30.9)	
Dual catheter access				
	Radial/Femoral	37 (22.4)	31 (18.8)	
	Femoral/Femoral	13 (7.9)	18 (10.9)	
	Radial/Radial	1 (0.6)	0 (0.0)	
Primary approach (%)				0.75
	Antegrade	141 (85.5)	144 (87.3)	
	Retrograde	24 (14.5)	21 (12.7)	
Recanalization technique (%)				0.67

Antegrade wire escalation	Single wire	132 (81.0)	134 (81.7)	
	Parallel wire	6 (3.7)	9 (5.5)	
Antegrade dissection re-entry	Mini STAR / LAST	2 (1.2)	0 (0.0)	
	crossboss/stingray	3 (1.8)	1 (0.6)	
Retrograde technique	Retrograde wire escalation	11 (6.7)	9 (5.5)	
	Kissing wire	4 (2.5)	3 (1.8)	
	Reverse CART	5 (3.1)	8 (4.9)	
Contrast (ml) ± SD*		n= 124	n= 120	
		223 ± 122	208 ± 96	0.31
Radiation DAP (Gycm2) ± SD*		n= 81	n= 82	
		155 ± 17	122 ± 14	0.47
Fluoroscopy time (min) ± SD*		n= 74	n= 80	
		25.9 ± 23.9	23.3 ± 19.6	0.47
Occlusion length (mm) mean ± SD		20.9 ± 14.5	20.4 ± 12.4	0.74
J-CTO score mean ± SD		1.8 ± 1.1	2.0 ± 1.1	0.03
J-CTO score risk group (%)				0.07
	0 = Easy	20 (12.1)	8 (4.8)	

	1 = Intermediate	52 (31.5)	49 (29.7)	
	2 = Difficult	50 (30.3)	52 (31.5)	
	3 ≥ Very difficult	43 (26.1)	56 (33.9)	
J-CTO variables				
Entry				0.05
	Blunt	63 (38.2)	88 (53.5)	
	Tapered			
	Triangular	10 (6.1)	6 (3.6)	
	String	79 (47.9)	61 (37)	
	Beads	13 (7.9)	10 (6.1)	
Calcification				0.42
	Absent	62 (37.6)	55 (33.3)	
	Mild	61 (37.0)	64 (38.8)	
	Severe	42 (25.5)	46 (27.9)	
Tortuosity > 45 degrees				0.78
	Yes	31 (18.8)	34 (20.6)	
	No	134 (81.2)	131 (79.4)	
CTO length ≥ 20 mm				0.44
	Yes	74 (44.8)	82 (49.7)	
	No	91 (55.2)	83 (50.3)	
Re-try lesion				0.87
	Yes	21 (12.7)	23 (13.9)	
	No	144 (87.3)	142 (86.1)	

Stent diameter (mm), mean ± SD	3.2 ± 0.4	3.2 ± 0.4	0.82
Stent balloon pressure, mean ± SD	15.7 ± 3.4	15.5 ± 3.2	0.63
Post dilatation (%)	58 (35.2)	57 (34.8)	0.99
Non-compliant balloon (%)	48 (29.1)	46 (27.9)	0.81
Post dilatation diameter (mm), mean ± SD	3.4 ± 0.5	3.5 ± 0.5	0.18
Post dilatation pressure (atm), mean ± SD	19.1 ± 4.1	18.4 ± 4.4	0.41
Maximal stent-/ post dilatation balloon diameter (mm), mean ± SD	3.3 ± 0.5	3.3 ± 0.5	0.88
Maximal stent- / post dilatation balloon pressure (atm), mean ± SD	16.8 ± 4.0	16.6 ± 3.7	0.55
Total stent length (mm), mean ± SD	52.4 ± 28.1	52.3 ± 26.6	0.96
Number of stents, mean ± SD	2.1 ± 1.1	2.0 ± 1.0	0.51
TIMI flow post procedure (%)*			0.70
O	0 (0.0)	1 (0.6)	
I	0 (0.0)	0 (0.0)	
II	2 (1.2)	1 (0.6)	
III	163 (98.8)	163 (98.8)	

Values are mean ± standard deviation (SD) and counts (%); *Not all data are complete for this variable; atm, atmosphere; CART, controlled antegrade and retrograde tracking; CTO, chronic total occlusion; DAP, dose area product; EES, everolimus-eluting stent; Gy, gray; LAST, limited

antegrade subintimal tracking; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; RCA right coronary artery; RCX, ramus circumflex; SES, hybrid sirolimus-eluting stents; STAR, subitimal tracking and re-entry; TIMI, thrombolysis in myocardial infarction.

Table 3. Periprocedural complications

	Hybrid Sirolimus (SES) n=165	Everolimus (EES) N=165
Pericardiocentesis	2	0
Donor artery dissection	1	1
Dissection distal coronary bed TIMI flow II TIMI flow III	 1 2	 1 1
Failed recanalization TIMI flow 0	0	1
Minor stroke	1	1
Vascular intervention	0	1

All values are number and percentages; EES, everolimus-eluting stents; SES, hybrid sirolimus-eluting stent; TIMI, trombolysis in Myocardial infarction grade flow.

Table 4. Angiographic outcome

	Hybrid Sirolimus (SES)	Everolimus (EES)	
Pre-procedure			
Occlusion length (mm)	20.4±12.4	20.9±14.5	0.74
Proximal RVD (mm)	2.55±0.98	2.63±1.05	0.51
After predilatation			
Proximal RVD (mm)	2.41±0.60	2.44±0.63	0.67
Distal RVD (mm)	1.74±0.57	1.72±0.56	0.66
MLD RVD (mm)	2.18±0.48	2.18±0.54	0.97
MLD (mm)	0.85±0.38	0.85±0.44	0.98
% diameter stenosis	60.19±16.96	60.89±16.89	0.72
Post procedure			
Proximal RVD (mm)	3.27±0.55	3.25±0.50	0.68
Proximal edge RVD (mm)	3.23±0.54	3.21±0.49	0.68
Proximal edge MLD (mm)	3.05±0.55	3.08±0.53	0.59
Proximal % diameter stenosis	5.40±9.66	3.92±8.11	0.13
Distal RVD (mm)	2.47±0.47	2.45±0.47	0.68
Distal edge RVD (mm)	2.52±0.45	2.51±0.45	0.77
Distal edge MLD (mm)	2.48±0.48	2.48±0.46	0.98
Distal edge % diameter stenosis	1.35±8.60	0.59±9.25	0.44
In-stent RVD (mm)	2.96±0.51	2.91± 0.46	0.33
In-stent MLD (mm)	2.40±0.42	2.37±0.41	0.60
In-stent % diameter stenosis	25.07±16.93	23.44±13.60	0.38
In-segment RVD (mm)	2.98±0.50	2.92±0.44	0.27
In-segment MLD (mm)	2.49±0.45	2.43±0.41	0.17
In-segment % diameter stenosis	23.36±17.76	20.80±13.87	0.18
9-month follow-up			
Proximal RVD (mm)	3.38±0.59	3.35±0.54	0.68
Proximal edge RVD (mm)	3.27±0.76	3.27±0.66	0.99
Proximal edge MLD (mm)	3.10±0.76	3.13±0.71	0.71
Proximal % diameter stenosis	5.20±8.27	4.21±10.48	0.38

Distal RVD (mm)	2.62±0.52	2.66±0.61	0.53
Distal edge RVD (mm)	2.62±0.62	2.67±0.66	0.50
Distal edge MLD (mm)	2.58±0.64	2.61±0.62	0.69
Distal edge % diameter stenosis	1.57±8.08	1.85±10.48	0.80
In-stent MLD, RVD (mm)	2.97±0.69	3.00±0.66	0.72
In-stent MLD (mm)	2.28±0.66	2.32±0.56	0.57
In-stent % diameter stenosis	25.07±16.93	23.44±13.60	0.38
In-segment RVD (mm)	3.04±0.55	3.05±0.50	0.85
In-segment MLD (mm)	2.35±0.69	2.42±0.57	0.36
In-segment % diameter stenosis	23.36±17.76	20.80±13.87	0.18
In-stent late luminal loss (mm)	0.12±0.59	0.07±0.46	0.52
In-segment late luminal loss (mm)	0.13±0.63	0.02±0.47	0.080
In-stent binary restenosis, n, (%)	11 (8.0)	3 (2.1)	0.028
In-segment binary restenosis, n, (%)	11 (8.0)	3 (2.1)	0.028
Reocclusions, n, (%)	3 (2.2)	2 (1.4)	0.68
In-stent restenosis lesion classification*			0.032
Focal type Ic	8 (5.8)	1 (0.7)	
Total occlusion, type IV	3 (2.2)	2 (1.4)	
Restenosis/reocclusion at previously occluded lesion	6 (4.4)	3 (2.1)	0.50

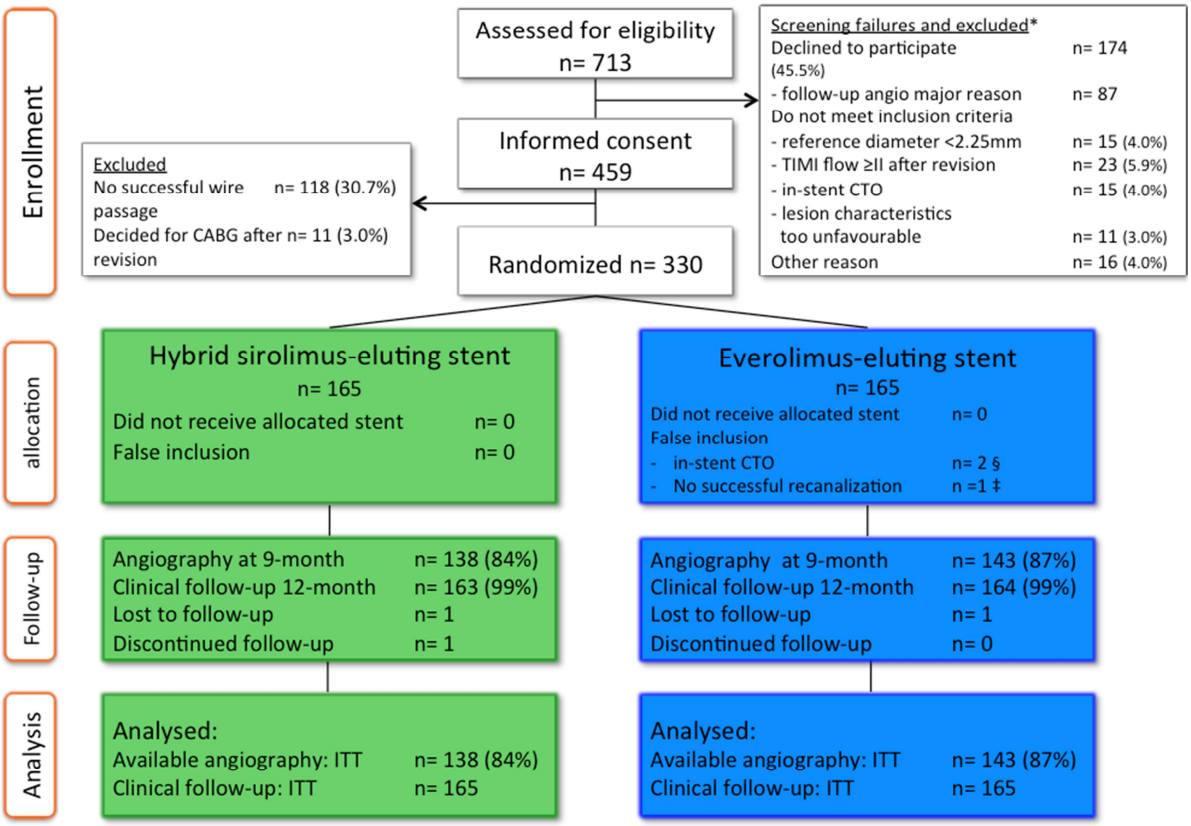
Values are mean ± standard deviation (SD), percentages ± SD and counts (%); *Mehran's in-stent restenosis lesion classification; EES, everolimus-eluting stent; SES, hybrid sirolimus-eluting stent; mm, millimeter; MLD, minimal luminal diameter; RVD, reference vessel diameter.

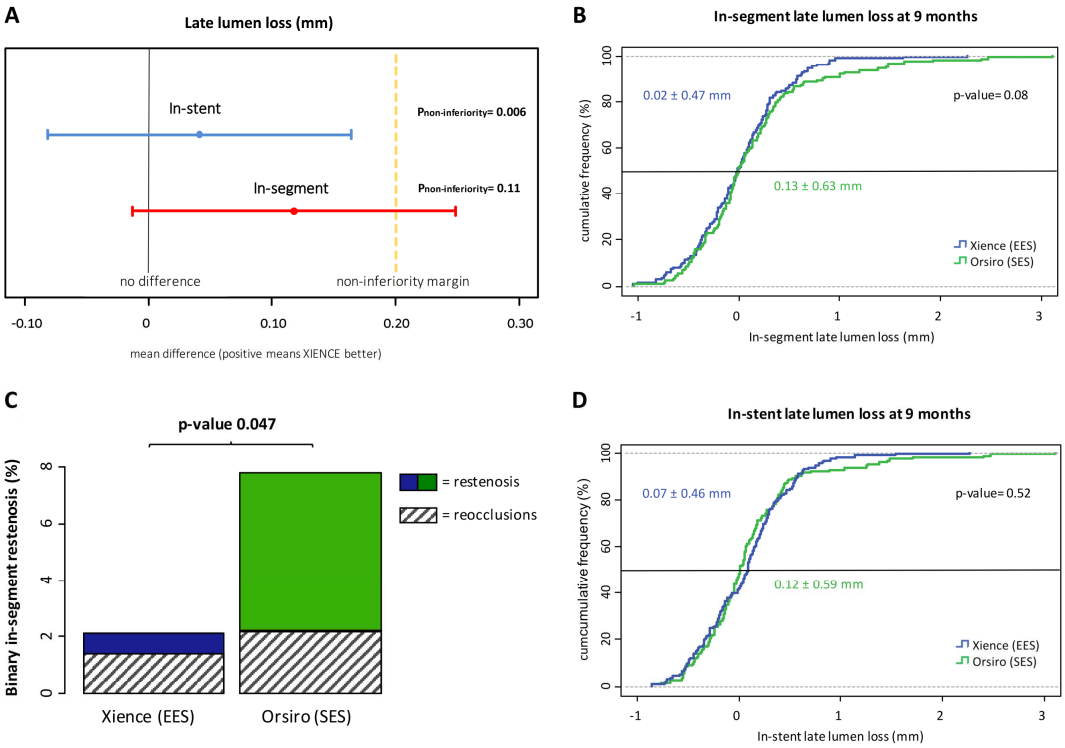
Table 5. Canadian Cardiovascular Society of Angina Grading and Clinical Events at 12 months

	Hybrid Sirolimus (SES) n=165	Everolimus (EES) n=165	
CCS Angina Grading at 12 months			0.60
0	154 (93.3)	148 (89.7)	
I	1 (0.6)	4 (2.4)	
II	5 (3.0)	10 (6.1)	
III	4 (2.4)	3 (1.8)	
IV	1 (0.6)	0	
Target lesion revascularization	16 (10.5)	6 (4)	0.04
Clinically driven	14 (9.2)	6 (4)	0.08
OCT driven	2 (1.4)	0	0.16
Target vessel revascularization, non-TLR	0	3 (2)	0.08
Non-target vessel revascularization	20 (12.3)	18 (11.1)	0.75
Planned	13 (7.9)	12 (7.3)	0.82
Unplanned	5 (3.5)	8 (5.3)	0.39
Myocardial infarction §	1	1	
Stent thrombosis			
Definite or probable	1	1	
Possible		1	
Timing			
Late*	1	2	
Death			
Cardiac	1	2	
Non-cardiac	0	1	
Composite end points			
Target vessel failure	15 (9.9)	10 (6.6)	0.35
Major adverse cardiac events	15 (9.9)	8 (5.3)	0.16

Number of patients with Canadian Society of Angina Grading (CCS) score 0, I, II, III, IV and % are reported and p-values are 2-sided calculated with fisher's exact; Number of events (Kaplan-Meier estimates at 365 days [%]) are reported and p-values are 2-sided calculated

with log-rank tests; *defined as stent thrombosis >30 days; §defined as the presence of new significant Q waves or an elevation of creatine kinase or its MB isoenzyme to at least twice the upper limit; EES, everolimus-eluting stent, non-TLR, non-target lesion revascularization; SES, hybrid sirolimus-eluting stent.





Appendix A

	angio follow-up	no angio follow-up	OR	p.ratio	p.overall	N
	N=281	N=49				
Randomization					0.536	330
Everolimus (XIENCE)	143 (50.9%)	22 (44.9%)	Ref.	Ref.		
Hybrid sirolimus (Orsiro)	138 (49.1%)	27 (55.1%)	1.27 [0.69; 2.36]	0.445		
Age	62.7 (9.85)	65.2 (10.5)	1.03 [0.99; 1.06]	0.114	0.133	330
Sex					0.265	330
Male	224 (79.7%)	35 (71.4%)	Ref.	Ref.		
Female	57 (20.3%)	14 (28.6%)	1.58 [0.77; 3.09]	0.205		
Angina_CCS_Baseline_3 or 4:					0.883	330
No	206 (73.3%)	37 (75.5%)	Ref.	Ref.		
Yes	75 (26.7%)	12 (24.5%)	0.90 [0.43; 1.77]	0.764		
Diabetes					0.314	329
No	228 (81.4%)	36 (73.5%)	Ref.	Ref.		
Yes	52 (18.7%)	12 (24.5%)	1.63 [0.76; 3.30]	0.205		
Vessel:					0.839	330
LAD	82 (29.2%)	16 (32.7%)	Ref.	Ref.		
CX	43 (15.3%)	8 (16.3%)	0.96 [0.36; 2.39]	0.934		
RCA	156 (55.5%)	25 (51.0%)	0.82 [0.42; 1.66]	0.572		
Previous myocardial infarction					0.324	330
No	195 (69.4%)	38 (77.6%)	Ref.	Ref.		
Yes	86 (30.6%)	11 (22.4%)	0.66 [0.31; 1.32]	0.252		
Previous PCI			0.364	329		
No	195 (69.4%)	37 (77.1%)				
Yes	86 (30.6%)	11 (22.9%)				
Previous CABG					0.485	330
No	265 (94.3%)	48 (98.0%)	Ref.	Ref.		
Yes	16 (5.69%)	1 (2.04%)	0.39 [0.02; 1.99]	0.311		
Occlusion duration > 3 months					0.147	330
No	24 (8.54%)	1 (2.04%)	Ref.	Ref.		
Yes	257 (91.5%)	48 (98.0%)	3.94 [0.80; 95.3]	0.103		
Antegrade =1/retrograde=2 approach					0.204	330
1	246 (87.5%)	39 (79.6%)	Ref.	Ref.		
2	35 (12.5%)	10 (20.4%)	1.81 [0.79; 3.87]	0.153		
Pre-procedural TIMI flow					0.227	330
0	258 (91.8%)	48 (98.0%)	Ref.	Ref.		
1	23 (8.19%)	1 (2.04%)	0.27 [0.01; 1.31]	0.119		
Occlusion length (mm)	20.7 (13.7)	20.4 (12.1)	1.00 [0.97; 1.02]	0.880	0.870	309
Total stent length	51.9 (27.6)	55.3 (25.8)	1.00 [0.99; 1.02]	0.412	0.392	330
J-cto_score.1 (mean (SD))	1.94 (1.11)	1.73 (1.08)	0.84 [0.63; 1.12]	0.231	0.225	330
J-cto_score:					0.202	330
0	20 (7.12%)	8 (16.3%)				

1	90 (32.0%)	11 (22.4%)				
2	85 (30.2%)	17 (34.7%)				
>3	86 (30.1%)	13 (26.5%)				
Post procedural segment reference diameter	2.63 (0.65)	2.58 (0.66)	0.90 [0.56; 1.46]	0.674	0.681	328
Post procedural in-stent % diameter stenosis (%)	18.3 (6.98)	20.3 (9.32)	1.03 [0.99; 1.08]	0.097	0.178	328
In-segment acute MLD gain (mm)	1.60 (0.56)	1.66 (0.62)	1.19 [0.68; 2.08]	0.543	0.576	309

Appendix B.