



STELLIUM 1: First-In-Man Follow-up Evaluation of Bioabsorbable Polymer-Coated Paclitaxel-Eluting Stent

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STELLIUM 1: First-In-Man Follow-up Evaluation of Bioabsorbable Polymer-Coated Paclitaxel-Eluting Stent

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Background: Durable polymers used for first-generation drug-eluting stents (DES) potentially contribute to persistent inflammation and late DES thrombosis. The vascular response to the Stellium™ stent, which is coated with an absorbable polymer for slow release of low-dose paclitaxel, was evaluated in the present study.

Methods and Results: The 37 patients with stable angina were implanted with 47 Stellium™ stents. Quantitative coronary angiography (QCA) was performed at baseline, and QCA and optical coherence tomography (OCT) were performed at 6 months post-implant. The primary endpoint was major adverse cardiac events (MACE). At 6 months, 1 case of MACE occurred because of total occlusion of a protected left main artery. In-stent and segment binary restenosis rates were both 0%. In-stent late loss was 0.19 ± 0.54 mm. Altogether, 5,564 struts were visualized by OCT and mean neointimal thickness was 150.03 ± 146.36 μ m. The number of well-apposed struts with and without neointima overlay was 5,135 (92.29%) and 396 (7.12%), respectively. Peri-strut low intensity was observed in 518 struts (9.31%).

Conclusions: This first-in-man study of the Stellium™ stent shows the promising possibility of bioabsorbable polymeric surface coating paclitaxel-eluting stents out to 6 months. The low rate of peri-strut low intensity suggests low cellular toxicity of the Stellium™ stent compared with the first-generation DES. (*Circ J* 2010; **74**: 2089–2096)

Key Words: Bioabsorbable polymer; Neointima; Optical coherence tomography; Paclitaxel eluting stents

Drug-eluting stents (DES) remarkably reduce angiographic restenosis and target lesion revascularization (TLR) compared with bare metal stents (BMS).^{1–5} Recent reports, however, suggest that durable polymers and/or drugs used for first-generation DES are potential contributors to persistent inflammation leading to late stent thrombosis (LST), a life-threatening complication.^{6,7}

Editorial p 2052

Paclitaxel is an anti-microtubule drug that inhibits cell proliferation and migration of smooth muscle cells and endothelial cells.⁸ Paclitaxel elution from coronary stents reduces neointimal growth; rapid release of high-dose paclitaxel, however, has induced toxic effects, such as medial cell necrosis

and late strut malapposition, in a pig coronary model.^{9,10}

The commercially available paclitaxel-eluting stent (PES), the Taxus™ stent, achieves controlled and slow release of paclitaxel and improves clinical outcomes in patients with coronary artery disease. The durable polymer coating and residual paclitaxel within the polymer, however, have raised concerns about long-term safety.

The Stellium™ stent (DISA Vascular Pty Ltd, Cape Town, South Africa) has a slow-releasing absorbable polymer with a low total dose of paclitaxel on a thin-strut cobalt chromium stent platform (ChromoFlex™). According to the preclinical study using porcine coronary arteries, suppression of neointimal proliferation at 1 month was followed by good neointimal growth at 3 months, a similar finding to that for BMS.¹¹ Theoretically, the Stellium™ stent should improve arterial

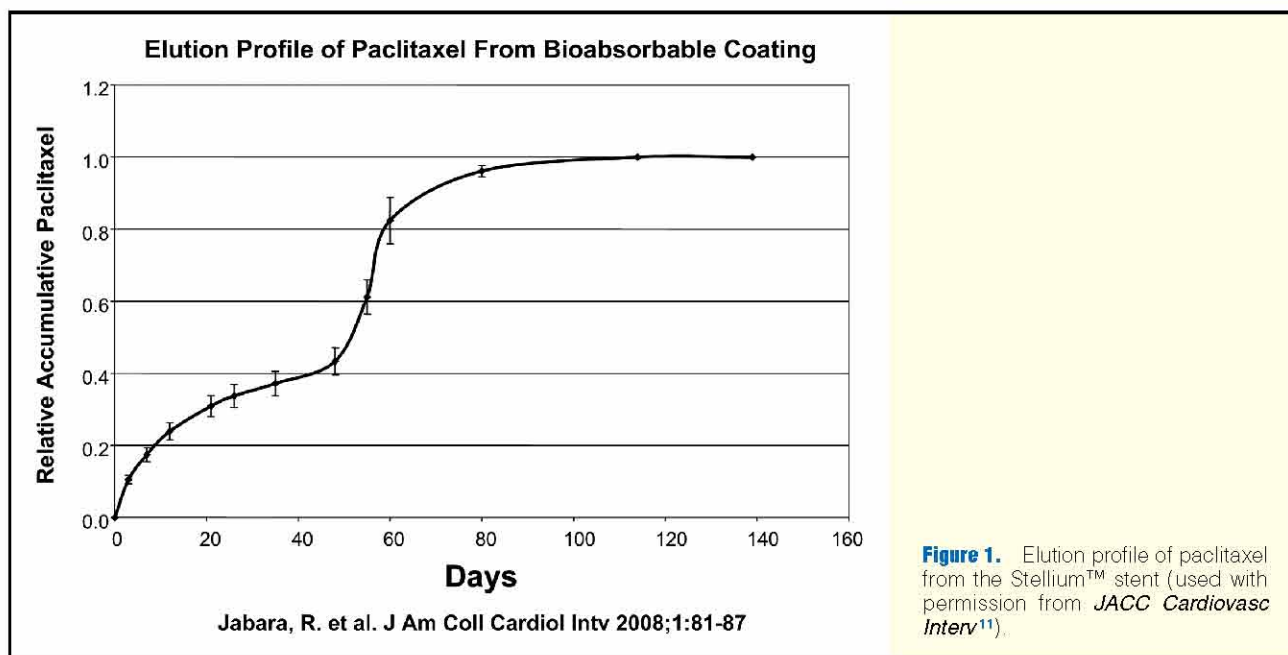
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healing and its features are expected to help reduce the risk of late thrombosis events while maintaining neointimal suppression.

Optical coherence tomography (OCT) is an imaging modality that can visualize intracoronary features with much higher axial resolution (10–20 μm) than intravascular ultrasound (IVUS: 100–150 μm).¹² OCT is reported to be superior for detecting stent apposition, neointimal stent coverage, and in-stent thrombosis.^{13–18}

The aim of the present study was to evaluate the efficacy and safety of the Stellium™ stent, based on a 6-month clinical follow-up with quantitative coronary angiography (QCA) and OCT in a subset of patients within the clinical study.

Methods

Stent Material

The Stellium™ stent has a thin-strut (75 μm) cobalt chromium stent platform coated with an erodible polymer carrier (<10 μm of thickness) with a very low total dose of paclitaxel (0.103 $\mu\text{g}/\text{mm}^2$). Drug release is relatively slow and comprises 2 phases: an initial mild burst-release for the first 20 days, which slows to produce a more gradual release by 50 days, and elution is complete by approximately 120 days (Figure 1). Poly(lactide-co-glycolide) (PLGA), a copolymer of polyglycolide and polylactide, which are aliphatic polyesters of poly (α -hydroxy acids) glycolic and lactic acid, is used as the biodegradable polymer for the stent. PLGA is hydrophilic and bulk erosion occurs via hydrolysis. The polymer is designed to be bioabsorbed within 4 months.

CE Marked ChromoFlex™ stents were coated by dissolving a fixed ratio of PLGA and paclitaxel (the drug was Good Manufacturing Practice grade, purity 99.7%). The polymer/drug mixture was sprayed onto the stents and dried until the stent reached a constant mass. Paclitaxel content was determined by gravimetric analysis with verification by coating dissolution and high-performance liquid chromatography.

The stents were 2.5 mm, 2.75 mm, 3.0 mm, or 3.5 mm in

diameter, and 11 mm, 14 mm, 17 mm, 20 mm, 24 mm, or 28 mm long.

Patients

The Stellium 1 study was a prospective, non-randomized, multicenter, single-arm trial in South Africa that was initiated to provisionally assess the efficacy and safety of the Stellium™ stent. We enrolled 37 patients with stable angina who met the eligibility criteria: age between 18 and 75 years; 1 or 2 de novo lesions in a native coronary artery with a reference vessel diameter between 2.5 and 3.5 mm; lesion length ≤ 28 mm; Canadian Cardiovascular Society functional class 2–4; positive functional test for ischemia; and negative troponin-T level. Exclusion criteria included overlapping stents, bifurcated stents, ostial lesions, unprotected left main lesions, and severely tortuous lesions.

Percutaneous Coronary Intervention Procedure

All patients were pretreated with 150 mg aspirin and 75 mg clopidogrel, and this regimen was continued for at least 12 months following treatment. Stents were premounted on a low-compliance delivery balloon catheter. Predilatation was mandatory, but post-dilatation was performed at the operator's discretion.

At 6 months, follow-up coronary angiography and OCT were performed in a subset of patients who were chosen because of their access to the OCT facilities and because they gave informed consent. The QCA and OCT analyses were performed by an independent core laboratory (Kobe University, Kobe, Japan).

QCA Analysis

Minimal lumen diameter (MLD), reference vessel diameter, and the severity of stenosis of the stented segment and the peri-stent segments (defined as 5 mm proximal and distal to the stent edge) were measured. Measurements were based on calibration of a contrast-filled catheter and automatic contour detection using a QCA cardiovascular measurement system (CMS-Medis Medical Imaging System, Leiden, the

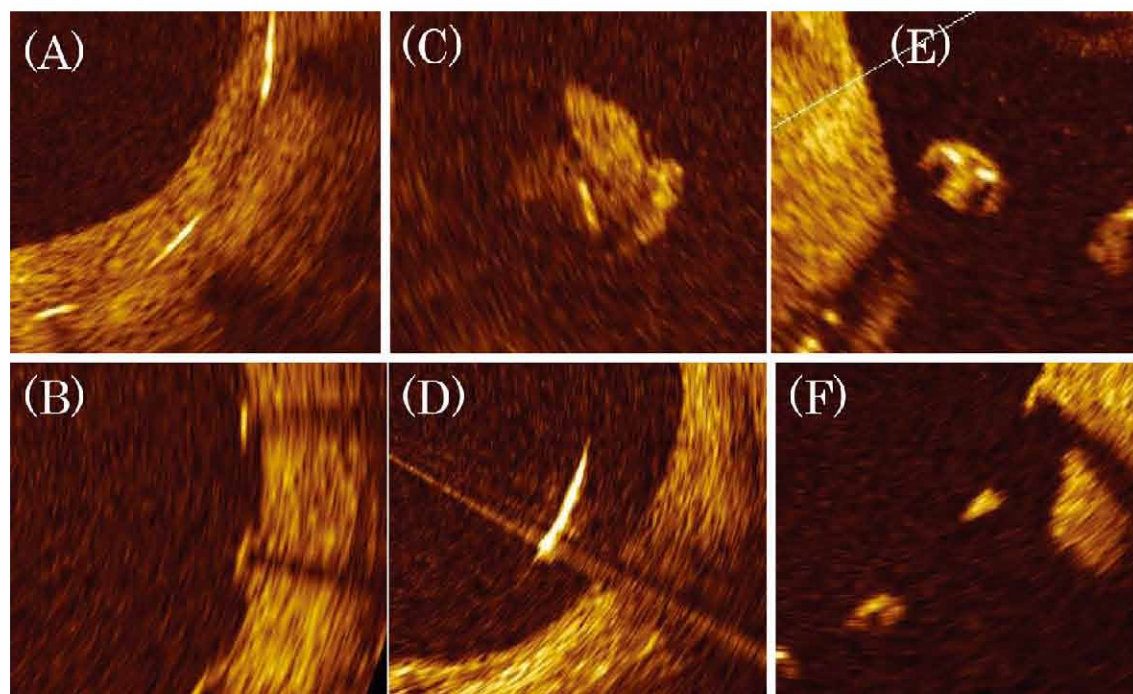


Figure 2. Stent struts classified into 6 categories: (A) well-apposed neointima, (B) well-apposed without neointima, (C) malapposed with neointima, (D) malapposed without neointima, (E) side branch/orifice site with neointima, (F) side branch/orifice site without neointima.

Netherlands). Acute luminal gain, late luminal loss, and loss index were defined as the difference between MLD after the procedure and MLD before the procedure, the difference between MLD at follow-up and MLD after the procedure, and late luminal loss divided by acute luminal gain, respectively.

OCT Examination

Through a 0.0014-inch angioplasty guidewire, an over-the-wire type occlusion balloon catheter (Helios™, Lightlab Imaging, Westford, MA, USA) was advanced to the distal end of each stent. The OCT imaging probe (Image Wire™, LightLab Imaging) was inserted through the occlusion balloon after removing the guidewire. With the Image Wire held in place, the occlusion balloon was withdrawn until proximal to the stent, where it was inflated to 0.5 atm and lactated Ringer's solution was infused from the distal tip of the occlusion balloon at 0.5 ml/s to clear red blood cells from the imaging site. The entire stent was imaged with an automatic pullback device moving at 1 mm/s. For large vessels in which the balloon occlusion method was inadequate, a non-occlusive flushing method with a pullback speed of 2 mm/s was used because it is compatible with the traditional method.^{16,19,20}

OCT Analysis

OCT images were analyzed by 2 independent observers who were unaware of the clinical presentations and lesion characteristics. The observers used proprietary off-line software provided by LightLab Imaging Inc. Cross-sectional images were analyzed at 0.5-mm intervals.

The OCT analysis included: (1) strut apposition to the vessel wall; (2) neointimal thickness on each strut surface;

(3) stent diameter; (4) lumen diameter; (5) stent cross-sectional area; (6) lumen cross-sectional area; (7) the ratio of uncovered struts to total struts per cross-section (RUST); (8) stent eccentricity index (SEI); (9) neointimal unevenness score (NUS); (10) frequency of peri-strut low intensity (PLI); and (11) mural thrombus. Based on their apposition to the vessel wall and neointimal coverage, stent struts were categorized as well-apposed with neointima (A), well-apposed without neointima (B), malapposed with neointima (C), malapposed without neointima (D), side-branch/orifice site with neointima (E), or side-branch/orifice site without neointima (F). Malapposition was defined as a greater than 100 μ m between the center reflection of the struts and the vessel wall surface,²¹ which was determined by adding the OCT axial resolution (20 μ m) to the actual stent strut thickness (80 μ m). Representative images are shown in Figure 2. RUST was calculated as the number of uncovered stent struts divided by the total number of struts at the same cross-section. RUST is reported to be the best morphometric predictor of LST.²² SEI was defined as the minimum stent diameter divided by maximum stent diameter. NUS was defined as the maximum neointimal thickness divided by the mean neointimal thickness of the same cross-section. PLI was defined as a contrasting lower intensity area compared with the adjacent surrounding neointimal tissue (Figure 3). We assumed that PLI represented the inflammatory response to the stent involving fibrin or proteoglycan. Intra-stent thrombus was defined as an irregular mass protruding into the lumen with significant attenuation behind the mass.^{14,15}

Primary Endpoint

The primary endpoint was a major adverse cardiac event

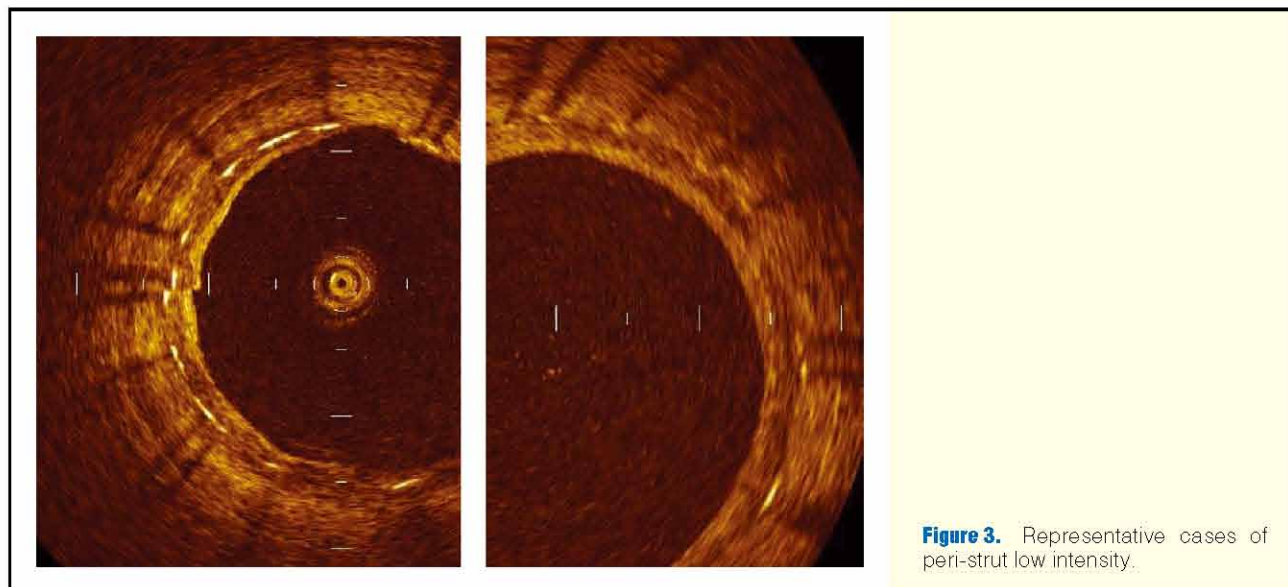


Figure 3. Representative cases of peri-strut low intensity.

Table 1. Baseline Clinical Characteristics

Patients	37
Age (years)	57±9
Male (%)	69
Hypertension (%)	66
Dyslipidemia (%)	57
Diabetes mellitus (%)	23
Smoking (%)	66
Prior MI (%)	6
Prior CABG (%)	14
Prior PCI (%)	9

MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

Table 2. Baseline Angiographic and Procedural Characteristics

LAD (%)	32
LCX (%)	23
RCA (%)	36
RAMUS (%)	2
Protected LMT (%)	7
Lesion class (AHA/ACC) (%)	
Type A	25
Type B	63
Type C	12
Predilatations done (%)	94
Average no. of stents per patient	1.3
Average stent length (mm)	18.25±5.53
Average stent diameter (mm)	3.17±0.34
Average pressure deployed (atm)	15.2
Postdilations done (%)	23
Average postdilatation pressure (atm)	16.7
% of procedural success (%)	98

Data are n or % unless otherwise shown.

LAD, left anterior descending; LCX, left circumflex artery; RCA, right coronary artery; LMT, left main trunk; AHA, American Heart Association; ACC, American College of Cardiology.

(MACE) at 6 months after stent implantation, including TLR, ST- or non ST-elevated myocardial infarction (STEMI or non-STEMI), stent thrombosis, or death.

The study was performed in accordance with the Declaration of Helsinki and was approved by the institutional ethics committees at the participating institutions. All patients provided written informed consent.

Statistical Analysis

Qualitative data are presented with frequencies and quantitative data are shown as mean values ± SD. To assess the inter- and intra-observer variabilities, the results were compared using the κ -test of concordance for the categorical data and Bland-Altman plot for continuous variables.

Results

Among the 37 patients enrolled in this study, 1 was enrolled despite major protocol violations, including overlap stenting of the protected left main artery at the ostium. Incomplete lesion coverage at the ostium in this case was judged to be the probable cause of subsequent occlusion of the stented segment, although the patient remained asymptomatic because of patent bypass grafts. This patient was not included in the QCA and OCT follow-up analysis because of the major protocol violations. One other patient had a failed stent implantation because of stent dislodgement during the procedure. The dislodged stent was crushed to the vessel wall using a BMS. The patient remained event-free for up to 6 months. OCT assessment of the crushed stent revealed moderate healing and a fully patent segment. This case was also not included in the OCT or QCA analysis because of the failed procedure.

The remaining 35 patients received a total of 44 stents, which were all successfully implanted. The mean stent length was 18.25±5.53 mm and the diameter was 3.17±0.34 mm. The baseline clinical and procedural characteristics are listed in **Tables 1** and **2**.

No cases of MACE were recorded during the hospital stay. At the 6-month follow-up, there was only 1 MACE (2.7%), which was the stent occlusion in the patient with multiple protocol violations. One patient underwent TLR to the distal

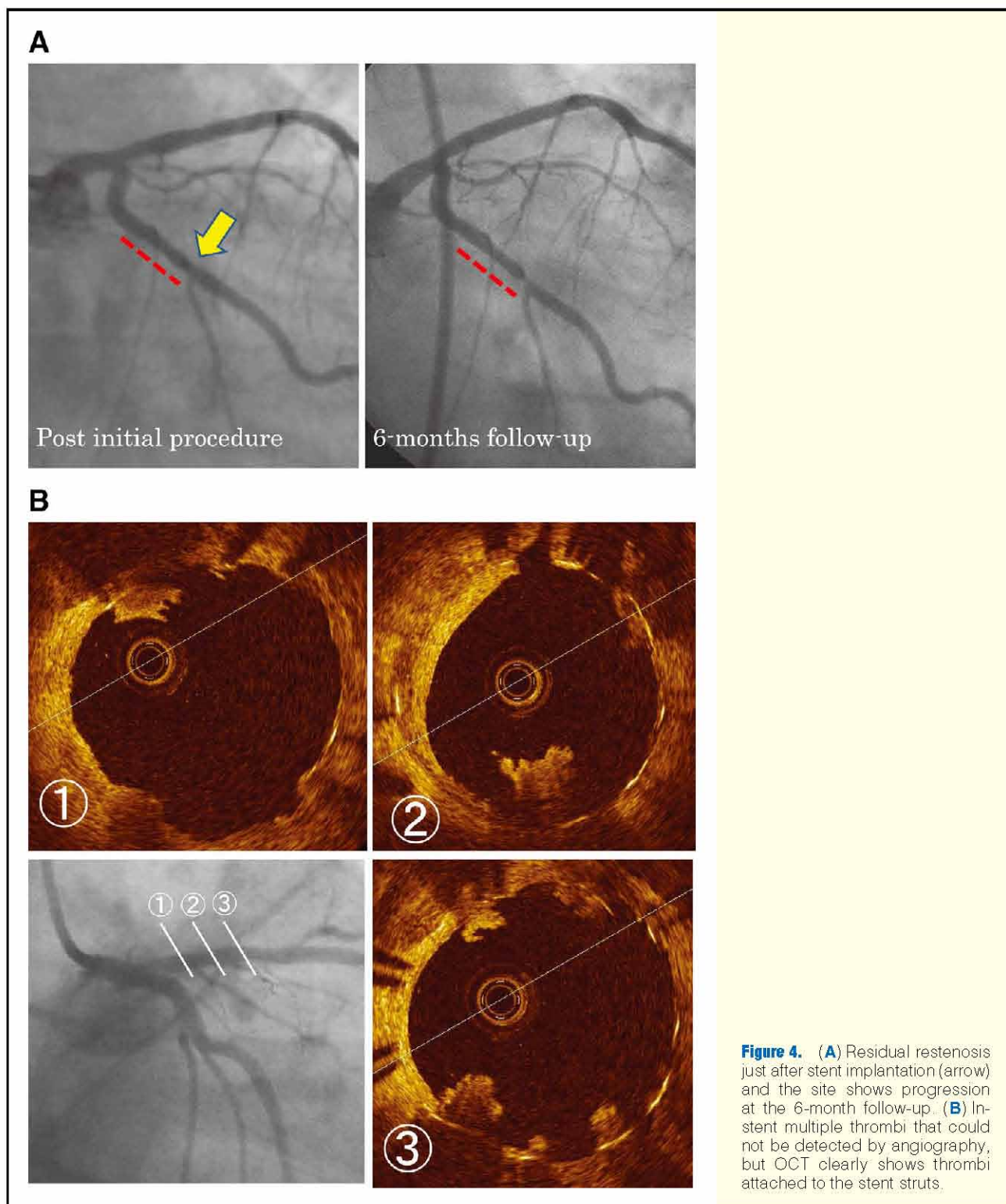


Figure 4. (A) Residual restenosis just after stent implantation (arrow) and the site shows progression at the 6-month follow-up. (B) In-stent multiple thrombi that could not be detected by angiography, but OCT clearly shows thrombi attached to the stent struts.

edge of the stent shortly after the 6-month follow-up cut-off. A zotarolimus-eluting stent was implanted (Figure 4A). No other MACE was reported.

QCA Results

QCA at 6 months was fulfilled in 16 cases (21 stents) and the data are shown in Table 3. The mean lesion length was 12.19 ± 4.64 mm. In-stent and analysis-segment binary restenosis were both 0%. In-stent loss was 0.19 ± 0.54 mm and analysis-segment late loss was 0.21 ± 0.55 mm.

OCT Results

OCT was fulfilled in 12 cases (15 stents) and the data are shown in Table 4. OCT visualized 5,564 struts and the mean neointimal thickness was 150.03 ± 146.36 μ m. The number of well-apposed struts with and without neointima overlay was

Table 3. Stent and Quantitative Coronary Angiographic Analysis

	Baseline	Postprocedure	6 months
Lesion length (mm)	12.19±4.64		
Reference vessel diameter (mm)	2.87±0.49	2.85±0.42	2.66±0.53
Minimal luminal diameter (mm)			
Analysis segment	0.90±0.32	2.50±0.49	2.23±0.49
Proximal edge		2.81±0.58	2.62±0.56
In stent		2.60±0.49	2.40±0.49
Distal segment		2.71±0.55	2.56±0.54
Stenosis (% of lumen diameter)			
Analysis segment	68.26±10.12	16.34±7.88	17.33±6.60
Proximal edge		9.20±6.54	11.99±6.69
In stent		14.03±7.04	15.34±10.22
Distal segment		8.17±10.27	7.07±5.76
Acute luminal gain (mm)			
Analysis segment		1.60±0.47	
Proximal edge		1.91±0.60	
In stent		1.70±0.44	
Distal segment		1.80±0.51	
Late loss (mm)			
Analysis segment			0.21±0.55
Proximal edge			0.19±0.66
In stent			0.19±0.54
Distal segment			0.15±0.64
Loss index			
Analysis segment			0.16±0.33
In stent			0.10±0.28
Binary-restenosis (%)			
Analysis segment			0
Proximal edge			0
In stent			0
Distal segment			0

Table 4. Optical Coherence Tomography Results

	n (%)
Total struts	5,564
Category of strut	
A: well-apposed with neointima	5,135 (92.29)
B: well-apposed without neointima	396 (7.12)
C: malapposed with neointima	9 (0.16)
D: malapposed without neointima	8 (0.14)
E: side-branch/orifice site with neointima	5 (0.09)
F: side-branch/orifice site without neointima	11 (0.20)
Mean neointimal thickness (μm)	150.03±146.36
Stents with all struts covered with neointima	3
RUST >0.3 (%)	8.54
RUST >0.3 per stent	3.06
Stent without RUST >0.3	6 stents (37.5)
NUS	2.17±0.55
PLI (%)	9.31
Stent area (mm ²)	7.89±1.89
Lumen area (mm ²)	6.18±1.89
% AS (%)	21.39±14.08
SEI	0.91±0.05

RUST, ratio of uncovered struts to total struts per cross section; NUS, neointimal unevenness score; PLI, peri-strut low intensity; AS, area stenosis (lumen area-stent area/lumen area); SEI, stent eccentricity index.

5,135 (92.29%) and 396 (7.12%), respectively. Of the 17 (0.30%) malapposed struts, 8 (0.14%) were not covered with neointima. Stent cross-sectional area, luminal cross-sectional area, and percent area stenosis were $7.89\pm1.89\text{ mm}^2$, $6.18\pm1.89\text{ mm}^2$, and $21.39\pm14.08\%$, respectively. RUST >0.3, a known predictor for LST, was observed in 8.54% of cross-sections. Six stents (37.5%) had no cross-section with RUST >0.3, 7 stents (43.2%) had only 1–4 cross-sections and 2 stents (12.5%) had more than 10 cross-sections.

PLI was observed in 518 struts (9.31%). Multiple thrombi attached to struts were observed in 1 stent, but neither angiographic obstruction nor clinical stent thrombosis was found (Figure 4B).

Discussion

The enthusiasm for the first generation of DES has been dampened by concerns about the long-term safety, especially the possibility of an increased risk of LST. Recent pathologic–histologic studies reported that rapid-release, moderate-to-high doses of paclitaxel and the durable polymer drug-carriers used for first-generation DES inhibit arterial healing, causing persistent fibrin deposits and incomplete endothelialization.^{23,24} Also, thick stent struts evoke TLR and may increase the risk of LST.

The Stellium™ stent is a cobalt chromium thin-strut platform covered by an erodible polymer that aids in the slow

release of a low dose of paclitaxel from the stent. The rationale behind a bioabsorbable polymer-coated stent is that it may improve the outcome if the coating is temporary and can degrade gradually and without inflammatory side-effects as the drug elutes, so that both the drug and polymer are no longer present in the artery wall once the anti-restenotic effect is achieved and the stented vessel is healed. The drug release from the Stellium™ stent is supposed to be completed by approximately 4 months, which is longer than other commercially available DES and novel biodegradable polymer coated drug-eluting stents: 1 month for PES, 48 days for the Supralimus™ stent²⁵ and 2 months for the Luc-Chopin™ stent.²⁶

The Stellium 1 study has shown promising clinical safety and efficacy of this design concept at the 6-month time-point. Only 1 major adverse event (2.7%) was recorded at the 6-month follow-up, which was stent occlusion in a patient who had been enrolled despite multiple protocol violations that were judged to be the likely cause of the occlusion. This frequency is comparable with the other biodegradable polymer DES.^{25,26} TLR in 1 patient shortly after the 6-month cut-off was judged to be possibly caused by suboptimal lesion coverage at the distal edge at the time of stenting.

Based on the QCA analysis, the 6-month binary in-stent and analysis-segment restenosis were both 0%, which compares well with permanent polymer-coated PES (0–8%),^{27,28} but the number of subjects in the present study was small.

In-stent late loss was low (0.19 mm), which was similar to that of sirolimus-eluting stents (SES: 0.17–0.2 mm),^{3,29} and less than that of PES (0.36–0.39 mm),^{27,28} zotarolimus-eluting stents (0.6 mm),³⁰ and BMS (>0.7 mm).

OCT analysis revealed that the mean neointimal thickness of the Stellium™ stent was $150 \pm 146 \mu\text{m}$, which was similar to that of PES ($148 \pm 163 \mu\text{m}$) and SES ($83 \pm 100 \mu\text{m}$),³¹ but thinner than BMS ($439 \pm 228 \mu\text{m}$) (unpublished data). Also, 99% of stent struts were apposed to the vessel wall (despite not using IVUS during any of the implantation procedures) and more than 90% (92.3%) were well covered with neointima. The extent of neointimal coverage was less than that of BMS (99%),³² but similar to that of PES (92.6%) and SES (85.8%).³¹

There is great interest in using OCT at stent follow-up to stratify the risk of LST, but because LST is a very rare event, there are as yet no confirmed OCT findings that predict its occurrence. Although a lack of neointimal coverage is reported to be a risk factor of mural thrombus, the presence of uncovered struts cannot yet be definitively identified as a risk factor of LST. We previously reported that intra-stent thrombus detected by OCT was related to stent length, the number of uncovered struts, SEI, and NUS.³³

A histopathologic study revealed that the ratio of uncovered to total stent struts per section (RUST) >0.3 was the best predictor of LST.²² Because this was based on histologic data from analysis of only 3 cross-sections per stent, we think that multiple consecutive cross-sections with RUST >0.3 might be a better predictor. Although caution is needed translating the data gained from different methods, we think that RUST >0.3 may be a good index in OCT analysis.

In the Stellium 1 study, RUST >0.3 was observed in 8.54% of cross-sections. There were 2 (12.5%) stents with more than 10 cross-sections of RUST >0.3 and they had more than 6 consecutive cross-sections. The other 13 stents had fewer than 4 cross-sections and no consecutive cross-sections. This might be a marker of LST risk and warrants further follow-up.

PLI is thought to represent delayed healing of the vessel wall around stent struts.³⁴ PLI was observed in only 9.31% of Stellium™ stent struts, which was surprisingly low compared with SES (17.0%) and PES (30.9%), as quantified in our previous studies.³¹

The efficacy of the Stellium™ stent has been reported from 1-month data in porcine coronaries (putatively equivalent to 6 months in humans) and similar safety to BMS was reported at 3 months (putatively equivalent to more than 1 year in humans).¹¹ The porcine histopathologic data suggests progressive stabilization and healing of the vessel after implantation of the Stellium™ stent, which may lead to improved long-term safety with a low rate of LST.

A concern about PES is that only 10% of the paclitaxel elutes from this stent during the therapeutic phase and 90% is reported by the manufacturer to remain locked in the polymer. It is more likely, however, that this 90% continues to leach out slowly over a very long period. The long-term safety of this high dose of residual paclitaxel is unknown, especially in cases of stent fracture. In the Stellium™ stent, more than 90% of the loaded paclitaxel is released within 50 days.

Long-term dual antiplatelet therapy is thought to be needed after DES implantation. The Stellium™ stent showed promising arterial healing in the porcine study, and may enable a reduction in the duration of antiplatelet therapy if the promising preliminary clinical safety data at 6 months is maintained over the long term.

Study Limitations

This study was a non-randomized study with a small number of patients with simple lesions underpowered for detecting the rate of MACE. Therefore, further large randomized studies will be needed to generalize this result. The follow-up was 6 months and may not be enough to capture all the adverse events, especially LST. Because neither IVUS nor OCT were performed just after stent implantation, there is a possibility that stent malapposition was because of inadequate stent deployment. OCT and QCA could not be done to all the patients. There is a possibility of selection bias.

Conclusion

This first-in-man study of the Stellium bioabsorbable polymeric surface coating thin cobalt chromium strut PES showed promising possibility in stable patients at 6 months. QCA and OCT data also showed great suppression of neointimal proliferation and a low frequency of peri-strut low intensity. Further investigation based on the Stellium 1 results and further larger trials with broader inclusion criteria are warranted.

Disclosure

Conflict of Interest: Damian Conway is an employee of DISA Vascular (Pty) Ltd.

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