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12-months results from the PRESTIGE study using sirolimus drug-eluting balloons in the treatment of complex BTK tibial atherosclerotic lesions in CLTI patients

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The PRESTIGE study (NCT04071782) is a physician-initiated pilot study assessing the SELUTION SLR™ (M. A. MedAlliance SA, Nyon, Switzerland) drug eluting balloon (DEB) in chronic limb threatening ischaemia (CLTI) patients with TASC II C/D tibial atherosclerotic lesions. Sirolimus is a potent antiproliferative agent that prevents smooth muscle cell activation and reduces inflammatory cell recruitment after vascular injury. Tibial angioplasty in the CLTI setting is dogged by high restenosis rates because of elastic recoil and neointimal hyperplasia (NIH) [1], and this accounts for increased clinically driven target lesion revascularization (CD-TLR) interventions and morbidity and reduces limb salvage rates [2]. SELUTION SLR™ elutes sirolimus into the arterial wall over a 90-day period to inhibit the restenotic and NIH processes [3]. PRESTIGE has previously shown good safety and efficacy data using SELUTION SLR™ at 6-months, a world's-first experience using sirolimus in the below-the-knee (BTK) arena [4]. The aim of this communication is to report 12-month outcomes.

PRESTIGE is a non-randomized, single arm, observational, multi-investigator, single center study from Singapore. 25 Asian patients (18/25, 72% Chinese; 33 lesions, 25 limbs) all with Rutherford Class 5 wound severity were included. The study was conducted in accordance with good clinical practice standards and the ethical principles of the *Declaration of Helsinki* and its amendments. The local Institutional Review Board approved this study (IRB number: 2019/2121). Written informed consent was obtained in accordance with institutional protocol from each patient. Demographics, lesion characteristics and procedural data have been previously reported along with inclusion/exclusion criteria [4]. 21/25 (88%) patients were available for 12-month analysis; there were 3 deaths and one major lower limb amputation through six months and were censored. Collected data included primary tibial patency, CD-TLR, amputation free survival (AFS), change in Rutherford classification, wound status, EQ-5D quality of life survey and Walking Impairment Questionnaire (WIQ).

Mean time to follow-up was 390 (±12) days. Table 1 shows sustained improvement in every measure other than WIQ at the 12-month timepoint compared to 6-months. Complete wound healing was achieved in 17/21 (81%) patients, Fig. 1.

Tibial patency, AFS, Rutherford score improvement and CD-TLR rates were all sustained through 6 to 12-months. Patient reported overall health status as measured by EQ-5D and WIQ were maintained at one year and remained significantly improved from baseline. This shows that the sustained drug release properties of SELUTION SLR™ afford continued health improvements that go beyond that which would be expected with a simple local transient delivery of drug or treatment with a plain balloon angioplasty.

The optimal treatment of diseased tibial arteries in the setting of CLTI has yet to be defined. Paclitaxel coated balloons (PCB) have been studied as promising alternative to conventional balloon angioplasty (CBA) in CLTI patients to minimise the risk of restenosis in the medium term but meta data did not show superiority of PCB over CBA in terms of binary restenosis, late lumen loss, TLR and major amputation rates [5]. Direct comparison of PRESTIGE outcomes with PCB in CLTI is difficult because this was not a RCT and the major RCTs performed to date have only included patients with less severe disease (shorter and fewer calcified lesions) and obviously included larger patient cohorts. Despite more complex atherosclerotic lesions and patient co-morbidities included in PRESTIGE, clinical results are favourable compared to the local PCB vs CBA SINGA-PACLI trial, which included CLTI patients with a similar demographic profile [6]; SELUTION SLR demonstrates better cumulative TLR (7.4% vs 20%), higher AFS (84% vs 59%) and better wound healing (82% vs 52%) rates through one year.

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Table 1
Patient demographics, procedural details, and outcomes.

Characteristics	*Baseline* $N = 25$ (%)	*6-months* $N = 21$ (%)	*12-months* N = 21 (%)
Age, mean (±sd)	63.7 ± 9.7	63.6 ± 10.2	63.6 ± 10.2
BMI, kg/m^2, mean (±sd)	24.4 ± 4.9	24.2 ± 5.3	24.2 ± 5.3
Male gender	17 (68.0)	15 (71.4)	15 (71.4)
Co-morbidities			
Smoker/Ex-smoker	9 (36.0)	8 (38.1)	8 (38.1)
Hypertension	22 (88.0)	18 (85.7)	18 (85.7)
Diabetes	22 (88.0)	18 (85.7)	18 (85.7)
Hypercholesterolemia	19 (76.0)	15 (71.4)	15 (71.4)
End Stage Renal Failure (ESRF)	11 (44.0)	9 (42.9)	9 (42.9)
Location of wound			
Digits	18 (72.0)	14 (66.7)	14 (66.7)
Forefoot	2 (8.0)	2 (9.5)	2 (9.5)
Heel	3 (12.0)	3 (14.3)	3 (14.3)
Shin	2 (8.0)	2 (9.5)	2 (9.5)

Treated lesions	*Baseline* $N = 33$ (%)
Location of Treated Vessel	
Anterior Tibial Artery (ATA)	17 (51.5)
Posterior Tibial Artery (PTA)	10 (30.3)
Common Plantar Artery	3 (9.1)
Dorsalis Pedis Artery (DPA)	3 (9.1)
Re-stenotic lesions	12 (36.4)
TASC Classification	
C	18 (54.5)
D	15 (45.5)
Mean length (mm), (±sd)	190.6 (±111)
Mean stenosis (%), (±sd)	88.9 (±12)
Moderate/Severe Calcification	21 (63.6)

Outcomes	*Baseline* N = 25 (%)	*6-months* N = 21 (%)	*12-months* $N = 21$ (%)
Death, subjects	–	3/25 (12.0)	–
Amputation Free Survival, subjects	–	21/25 (84.0)	21/25 (84.0)
Freedom from TLR, lesions	–	25/27 (92.6)	25/27 (92.6)
Complete wound healing, subjects	–	18 (85.7)	18 (85.7)
Rutherford			
0	–	16 (76.2)	16 (76.2)
1	–	1 (4.8)	1 (4.8)
2	–	–	1 (4.8)
3	–	1 (4.8)	–
4	–	–	–
5	25 (100)	3 (14.3)	3 (14.3)
Rutherford Improved by ≥1 category	–	18 (85.7)	18 (85.7)
Mean (±sd)	5.00	0.900 (±1.84)*	0.857 (±1.80)*
Mean WIFi Score (±sd)	3.72 (±1.12)	0.571 (±0.507)*	0.571 (±0.507)
Quality of life scores, mean (±sd)			
EQ5D TTO SG	0.631 (±0.309)	0.849 (±0.223)*	0.853 (±0.195)*
EQ5D VAS	58.0 (±9.57)	78.4 (±9.43)*	78.1 (±11.3)*
WIQ Distance Score	33.4 (±30.4)	39.3 (±26.8)	34.1 (±21.7)
WIQ Speed Score	22.8 (±16.8)	36.6 (±23.1)*	33.5 (±18.1)
WIQ Stairs Score	36.2 (±34.9)	37.3 (±27.6)	32.9 (±22.4)

TLR: Target Lesion Revascularisation.
WIFi: Wound, Ischaemia, Foot infection.
EQ-5D TTO SG: EuroQol-5 Dimension Time Trade-Off Singapore;.
EQ-5D VAS: EuroQol-5 Dimension Visual Analogue Scale. WIQ: Walking Impairment Questionnaire.
* Significant at $p < 0.05$ when compared to baseline values.

Our experience using the *Selution SLR™* balloon has been excellent trackability over the 0.018″ wire platform with short inflation and deflation times. There was no balloon slippage during inflation. There were good visible markers on the balloon to allow accurate placement prior to balloon inflation. There were no slow flow phenomenon encountered after sirolimus elution even with the balloon placed below the ankle in significant number of cases (40%) and there were no serious adverse events reported using the balloon during the first 30 days [4]. Slow flow phenomenon has been associated with a worse clinical outcome if encountered during drug coated angioplasty using paclitaxel platforms and the pathophysiology is thought to be related to particulate embolization into the microvasculature of the foot causing vasospasm or blockage [7]. This may be critical in the CLTI setting, where there may be already concomitant microvascular disease in the foot and outflow reserve severely limited. Sirolimus coated balloons may have an advantage over PCB use in the peripheral vasculature because of a reduced incidence of slow flow phenomenon following drug elution and this may be reflected in the sustained effect of wound healing and low TLR rates seen at one year.

Although PRESTIGE was a single arm, non-randomized study, with a relatively small sample size with a self-adjudicated policy, it demonstrated sustained efficacy and relative safety at 12-months when treating TASC II C/D tibial arterial occlusive lesions in CLTI patients using the SELUTION SLR™ sirolimus balloon platform. However, without a randomized control group for comparison, this study cannot provide definitive information about the safety or efficacy of this new

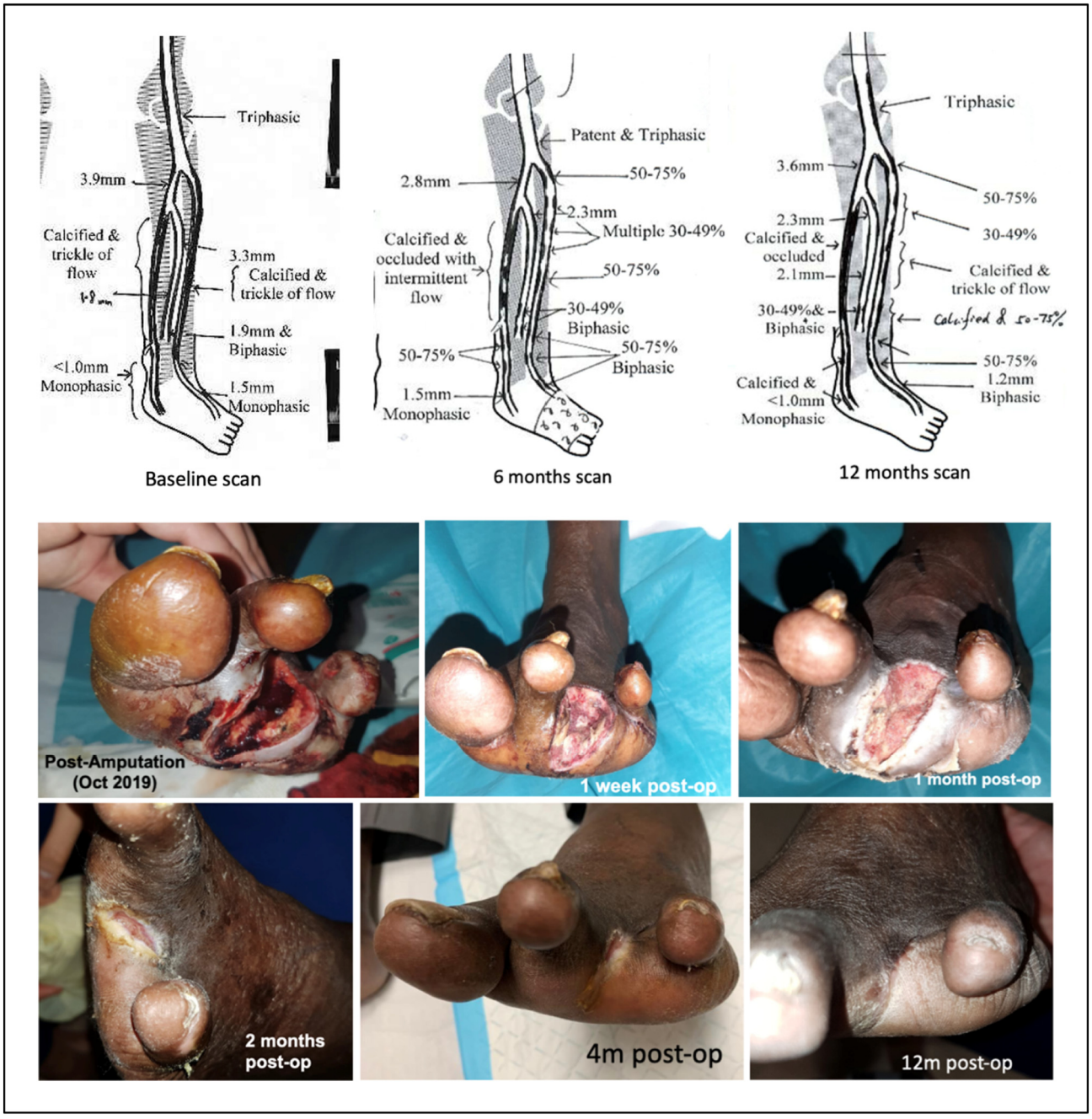

Fig. 1. Wound healing progress of a *PRESTIGE* study subject. The angiosome was based on the anterior tibial artery, which was occluded at presentation and remained open at the 6- and 12-month intervals after revascularization. The wound had healed by 4 months and remained closed at one year.

therapy in relation to CBA or PCB use. Larger randomized controlled trials are now required to test its use in the BTK arena in the setting of critical limb ischaemia.

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Declaration of competing interest

TYT has received honoraria from Biotronik, Philips, iVascular, Medtronic and Bard BD. His institution has received research and clinical trial study funds from Abbott Vascular, Bard BD, Biotronik, Boston Scientific, iVascular, M. A. MedAlliance and Medtronic.

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