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# Endovascular salvage of failing arterio-venous fistulas utilising sirolimus eluting balloons: Six months results from the ISABELLA trial

**Tjun Y Tang[1,2], Shereen XY Soon[1], Charyl JQ Yap[1], Ru Yu Tan[3], Suh Chien Pang[3], Ankur Patel[4], Apoorva Gogna[4], Chieh Suai Tan[3] and Tze Tec Chong[1]**

## Abstract

**Background:** Aim of this pilot clinical study was to evaluate the safety and efficacy of the *Selution Sustained Limus Release (SLR)*™ sirolimus-eluting balloon (SEB) for improving failing arterio-venous fistulas (AVF) patency in Asian haemodialysis patients.

**Methods:** Prospective single-centre, multi-investigator, non-consecutive, non-blinded single arm trial. Forty end-stage renal failure Asian patients with a dysfunctional AVF underwent SEB angioplasty between May and November 2020. All stenotic lesions were prepared with high pressure non-compliant balloon angioplasty prior to SEB angioplasty. Endpoints of interest included target lesion primary patency and circuit access patency and safety through 30 days. All patients received dual antiplatelet therapy for 1 month and were followed up with Duplex ultrasound at 6 months.

**Results:** There was one subject dropout so final $n = 39$ patients (mean age $65.0 \pm 11.9$; males = 26 (66.7%)) and $n = 43$ target lesions treated. Main indication for intervention was dropping access flow (24/39; 61.5%) and most common target lesion was in the juxta-anastomosis (24/43; 54.5%). There was 100% technical and procedural success. There were no adverse events related to the SEB. Target lesion primary patency rates at 3 and 6 months were 39/41 (95.1%) and 28/39 (71.8%) respectively. Access circuit patency rates at 3 and 6 months were 35/37 (94.6%) and 22/35 (62.9%) respectively. There were 3 (7.7%) deaths all attributable to patients' underlying co-morbidities.

**Conclusions:** Fistuloplasty using the novel *Selution SLR*™ SEB for dysfunctional AVF circuits seems a safe and effective modality in Asian haemodialysis patients at 6 months but larger randomised controlled studies are required now to determine its true efficacy against plain balloon angioplasty.

## Keywords

Sirolimus coated balloon, target lesion primary patency, arterio-venous fistula, outcome, safety

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## Introduction

Conduit stenosis is the commonest cause of a dysfunctional arterio-venous fistula (AVF) in haemodialysis (HD) and remains a significant cause of morbidity and hospital admissions for HD dependent end-stage renal failure (ESRF) patients.[1] The recently updated 2020 Kidney Dialysis Outcomes Quality Initiative guidelines recommend treating access stenotic lesions of 50% or more when clinically associated with reduced fistula flow rate and elevated venous pressures.[2]

[1]Department of Vascular Surgery, Singapore General Hospital, Singapore
[2]Duke NUS Graduate Medical School, Singapore
[3]Department of Renal Medicine, Singapore General Hospital, Singapore
[4]Department of Vascular Interventional Radiology, Sengkang General Hospital, Singapore

**Corresponding author:**
Tjun Y Tang, Duke-NUS Medical School, Department of Vascular Surgery, Singapore General Hospital, Academia, 20 College Road, Singapore 169856, Singapore.
Email: tang.tjun.yip@singhealth.com.sg

Percutaneous transluminal angioplasty (PTA) with high-pressure non-compliant balloons is the current endovascular gold standard of care for treatment of venous stenosis but primary access patency rates following plain balloon angioplasty (POBA) are low, achieving at best a 40%–50% 12-month primary target lesion patency,[3] with high recurrent stenosis rates, necessitating reinterventions and potential risk of circuit patency demise.[4] Neo-intimal hyperplasia (NIH) is understood to be the underlying pathophysiological mechanism responsible for restenosis and is thought to be related to endothelial injury caused not only by the barotrauma during PTA and repeated needle-stick injuries during HD, but also to the haemodynamic changes when the AVF becomes arterialised, leading to medial wall hypertrophy.[5] Furthermore, factors such as uraemia, oxidative stress and the pro-inflammatory state, which can cause endothelial dysfunction in the setting of ESRF, are thought to contribute to luminal re-narrowing.[6]

Drug coated balloon (DCB) angioplasty, using a paclitaxel-based platform (PCB), was introduced to offset the NIH phenomenon and reduce the risk of recurrent dysfunction and prolong access patency.[7] Paclitaxel is a cytotoxic antiproliferative agent that stabilises the microtubule cytoskeleton leading to cell apoptosis, reducing the restenotic process.[8] This has yielded satisfactory results in both the coronary bed[9] and peripheral vasculature[10] but the data in the setting of AVF to date is ambiguous. A meta-analysis performed by Khawaja et al.[11] seemed to suggest that DCBs conferred some benefit in terms of improving target lesion primary patency (TLPP) in AVFs. An updated meta-analysis performed recently by our group reinforced that PCB appears to be a better and safe alternative to POBA in treating patients with stenosis within all haemodialysis circuits (fistulas and arterio-venous grafts) based on 6- and 12-months primary patency and increased re-intervention free period.[5] However, this was not reflected in the largest RCT to date of PCB versus POBA in AVF with no improved target lesion patency demonstrated with PCB at 6 months and at 1 and 2 years follow-up.[12] One large RCT from the UK, which was unique in that it was not industry sponsored, comparing POBA versus PCB use in AVF also did not meet their primary endpoint in favour of PCB.[13] Hence this shows the data heterogeneity of PCB use in AVFs and the result is dependent on what studies you include in the review, the type of access circuits and the PCB device used. Another reason why the outcome data is variable is that the high-speed blood flow in dialysis access circuits washes a large amount of the paclitaxel away from the target lesion soon after application. A measurement in swine models showed that only up to 30% of paclitaxel was absorbed into the coronary artery wall in vivo 15–25 min after PCB application.[14]

Sirolimus, like paclitaxel, is a potent antiproliferative agent albeit cytostatic in nature, which has been found to prevent restenosis in the coronary bed[15] and more recently in the peripheral vasculature.[16] Sirolimus short-term effectiveness and safety in dialysis access circuits has shown promise in small pilot studies, albeit without a competitor balloon platform, in AVF dysfunction[17] and in salvaging thrombosed arterio-venous grafts.[18]

The aim was to determine the safety and efficacy of the *Selution Sustained Limus Release (SLR)*™ 018 sirolimus eluting balloon (SEB) (M.A. MedAlliance SA, Nyon, Switzerland), in the treatment of failing AVF circuits due to conduit stenosis in patients undergoing haemodialysis.

## Materials and methods

### Study design

The **I**ntervention with **S**elution SLR™ **A**gent **B**alloon for **E**ndovascular **L**atent **L**imus therapy for failing **A**V Fistulas **(ISABELLA)** Trial was a prospective single-centre, multi-investigator, non-consecutive, non-blinded single arm study investigating the safety and feasibility of the *Selution SLR*™ SEB for the treatment of failing AVF in haemodialysis patients. The hypothesis was that use of the SEB to cover the target stenotic lesion after successful preparatory effacement using a high pressure non-compliant balloon, minimises restenosis and improves AVF target lesion patency compared to historical POBA data.

The trial was carried out under an investigational device exemption (GN27) from the local Health Services Authority (HSA) of Singapore. Approval was obtained from the local Human Research Ethics Committee (CIRB ref: 2020/2782) and the study was carried out in accordance with the *Declaration of Helsinki*. Informed consent was gained from all participants. The protocol along with novel pre-clinical pharmacokinetic and histological data, to justify its endovascular utility has been recently published.[19]

ISABELLA is registered on *Clinicaltrials.gov* (NCT04629118).

### Study characteristics

Forty ESRF patients with a failing AVF on follow-up with the Departments of Vascular Surgery and Renal Medicine at Singapore General Hospital were recruited between May and November 2020. The aim was to include a patient population that reflected everyday vascular access salvage practice in Singapore. Patient demographics, clinical presentation, vascular access history, operative details and treatment outcomes were collected prospectively. The main inclusion criterion was a native mature AVF in the arm or forearm, which had at least one clinical indicator of dysfunction as defined by KDOQI.[2] Thrombosed and immature AVFs, previously stented circuits, presence of central venous stenosis, and arterio-venous grafts were excluded. The target lesion stenosis had to be initially treated successfully (residual stenosis $\leqslant$30% by angiographic measurement) with a high-pressure

POBA prior to SEB treatment. One additional ("nontarget") lesion in the access circuit was allowed to be included and had to be also successfully pre-treated (⩽30% residual stenosis) before SEB use. Separate lesion was defined as being at least 3 cm in distance from the target lesion. Reference vessel diameters allowed were 4–7 mm because of SEB size limitation. Patients were excluded if they were currently participating in another investigational device study involving sirolimus or paclitaxel that had not reached primary endpoint, had allergies to iodinated media contrast, heparin or sirolimus, had limited life expectancy (<12 months) to allow for completion of procedure and follow-up protocol and had contraindication to aspirin or clopidogrel use.

### Device under investigation

The *Selution SLR*™ DCB is a low dose (1 μg/mm$^2$) SEB. The drug coating has sirolimus-loaded bioresorbable poly(lactic-co-glycolic acid) (PLGA) microspheres, which allows for sustained release of sirolimus at the treatment site, as the smaller drug molecule diffuses through the polymer network. The coating formulation is sprayed onto the inflated balloon surface with a proprietary Cell Adherent Technology (CAT™) amphipathic transfer membrane that contains and protects the microspheres during balloon sheath entry, lesion crossing, and inflation. Upon contact with the vasculature, increased absorption of sirolimus into the vessel wall is helped by the coating amphiphatic properties. The SEB is designed for use with an 0.018-inch wire and was available in sizes 4 to 7 mm in diameter with 40–150 mm balloon lengths and 150 cm shaft length.

### Procedure and adjuvant medical therapy

All procedures were performed by either a vascular or interventional radiologist/nephrologist, under local anaesthesia and as a day case intervention. Description of how the procedure was performed has been previously detailed[19] but in summary, the access circuit was accessed via the conduit in all cases and stenosis was crossed with a 0.018-inch V18 guidewire (Boston Scientific, Marlborough, MA, USA), and pre-dilated with a standard high-pressure non-compliant balloon (Mustang®, Boston Scientific, Marlborough, MA, USA), to match the diameter of the adjacent normal vessel. The balloon was inflated to a pressure enough to efface the lesion and maintained invariably for 2 min. All lesions required at least balloon nominal pressure to be reached and generally moreover to fully efface the lesion. If a stenosis persisted along with recoil on the subsequent fistulogram, this was excluded from SEB use but this scenario only occurred in one case, which was subsequently stented. *Selution SLR*™ was subsequently implanted and inflated for 2 min at rated burst pressure (10 atm) to allow maximal drug transfer to the vessel wall. Balloon length was chosen so that it was 2 cm longer than the area treated during pre-dilatation (1 cm overlap proximal and distal) to avoid geographical miss. No post-dilatation was allowed with POBA and only a further SEB of same size diameter was used if required. Post procedure, all patients received daily aspirin (100 mg) and clopidogrel (75 mg) plus a proton pump inhibitor for 1 month followed thereafter with a single antiplatelet agent (APA).

### Endpoints and follow-up

The primary efficacy end point was target lesion primary patency (TLPP) at 6 months defined as freedom from clinically driven reintervention of the target lesion or access thrombosis and no significant restenosis (lumen diameter < 2.7 mm) on Duplex ultrasound.[20] The primary safety endpoint was defined as freedom from localised or systemic serious adverse event(s) involving the dialysis access circuit through 30 days These would include life-threatening events or those resulting in death, requiring hospitalisation, resulting in permanent disability, or requiring intervention to prevent permanent impairment; the latter definition including access thrombosis.

Secondary endpoints included TLPP at 3 months and access circuit primary patency at 3 and 6 months. Access circuit patency loss was defined by a development of a stenosis in any region of the AVF circuit requiring reintervention. Other secondary endpoints included technical (defined as the successful implantation of the SEB with <30% residual angiographic stenosis) and procedural success (defined as technical success with at least one indicator of hemodynamic or clinical improvement i.e. improvement in access circuit flow rate and can dialyse subsequently without problems), access circuit thrombosis, need for open bypass or revision surgery, access site abandonment, number of interventions required to maintain access circuit primary patency at 3 and 6 months and mortality.

All patients were followed-up by a telephone call from one of the study co-ordinators, to assess 1-month patency, any complications such as localised infection and hematoma of the AVF, compliance to antiplatelet therapy and to identify any adverse effects of treatment. Three and six-month clinic assessments were also performed with a dedicated Duplex ultrasound at 6 months. If a patient experienced an access problem, such as decreased dialysis flow rate, cannulation difficulty, recirculation and abnormal limb swelling in between follow-up visits, they underwent urgent Duplex scanning and clinical assessment in view for further endovascular intervention.

### Sample size calculation and statistical analysis

Based on a historical 6-month primary patency of POBA of approximately 50%,[3] we hypothesise that 6-month TLPP will improve to 70% following SEB. The estimated sample size needed was $n=28$ patients, using an alpha risk of 0.05

and a power of 0.8. Hence a follow-up of $n=40$ at 6 months would allow for dropouts. Baseline variables were summarised with the use of descriptive statistics. Continuous variables were reported as the mean and standard deviation, or median and range, as appropriate, and categorical variables as absolute number and percent. Univariable analysis for continuous and categorical variables were performed using Mann-Whitney *U* test and Fisher's exact tests respectively. The probability of re-intervention over time was calculated using competing risks analysis using the *cmprsk* package in R, as death was a competing risk. Patency was presented as Kaplan–Meier curves and compared using the paired log-rank test. *p* Values of less than 0.05 were considered to be statistically significant. Cause-specific sub-distributions was compared across groups using Gray's test. All analyses will be performed in R version 3.5.1.[21]

## Results

### *Patient demographics*

Forty ESRF patients (43 target lesions; 47 SEB used) were treated with combination high pressure POBA and SEB inflation over 6 months. There was one drop out from the study, which left *n* $n=39$ for analysis. There were 26 (66.7%) males and the mean age was $65.0 \pm 11.9$ years. Majority of patients were Chinese (28/39; 71.8%) and 30/39 (76.9%) were diabetic. 25/39 (64.1%) were on an APA at baseline. The majority of AVFs were radiocephalic (56.4%) and brachiocephalic (38.5%) fistulas. 29/39 (74.4%) had previously undergone POBA of their AVF and 10/39 (25.6%) AVFs had a history of access thrombosis. The median access age at time of dysfunction was 39.5 (IQR 18.1–90.6) months. Baseline demographics are shown in Table 1.

Main indications for intervention were dropping access flow in 24/39 (61.5%) circuits and high venous pressures during haemodialysis in 5/39 (12.8%). Main location of target lesion was in the juxta-anastomosis (defined as within 5 cm length from the anastomosis) 24/39 (54.5%). The most used size SEB was 7 mm (32/47; 68.1%). Indications and details regarding intervention are presented in Table 2. Technical and procedural success was 100%. There was no conduit rupture during any of the interventions requiring bailout stenting. There was no puncture site haemorrhage or infection requiring treatment or readmission. Bruising was observed along the circuit track in 6/39 (15.4%) patients, all had resolved at the 1-month telephone follow-up. There were no serious adverse events reported within 30 days that could be attributable to the procedure or SEB. There were 3 (7.7%) deaths (at 2.3, 4.6 and 5.2 months) at the 6 months interval and one AVF abandoned at day 16 post procedure (Table 3).

39/40 (97.5%) were available for 3- and 6-months follow-up. Overall mean follow-up was $6.8 \pm 1.4$ months (range 0.5–7.2 months). During that time all patients used their AVF for haemodialysis and did not require a temporary jugular or femoral HD catheter. Mean time to circuit reintervention was $3.5 \pm 1.4$ months and mean time to TLR was also $3.5 \pm 1.4$ months. Further interventions were required in three patients at 3 months and a further 12 patients by 6 months making a total of 15/39 (38.5%) by 6 months (Table 4). Of the 15 circuits re-intervened on, six circuits involved the use of further DCB (five PCB, one SEB) and one target lesion (cephalic arch) was stented.

**Table 1.** Patient demographics.

| | Number of subjects ($n=39$) | Percentage |
|---|---|---|
| Mean age, years (±SD) | $65 \pm 11.9$ | |
| Mean BMI, kg/m$^2$ (±SD) | $25 \pm 4.2$ | |
| Gender | | |
| Male | 26 | 66.7 |
| Female | 13 | 33.3 |
| Ethnic group | | |
| Chinese | 28 | 71.8 |
| Malay | 7 | 17.9 |
| Indian | 4 | 10.3 |
| Smoker | 5 | 12.8 |
| Co-morbidities (%) | | |
| Hypertension | 36 | 92.3 |
| Diabetes | 30 | 76.9 |
| Hyperlipidaemia | 27 | 69.2 |
| Coronary artery disease | 24 | 61.5 |
| Cerebrovascular accident | 7 | 17.9 |
| Medical history | | |
| Beta blocker | 28 | 71.8 |
| Statin | 27 | 69.2 |
| Antiplatelet | 25 | 64.1 |
| Antidiabetic agents | 20 | 51.3 |
| Warfarin | 3 | 7.7 |
| Access side | | |
| Left | 33 | 84.6 |
| Right | 6 | 15.4 |
| Access type | | |
| Radiocephalic | 22 | 56.4 |
| Brachiocephalic | 15 | 38.5 |
| Brachiobasilic | 1 | 2.6 |
| Ulnarbasilic | 1 | 2.6 |
| Median access age, months (IQR) | 39.5 (18.1–90.6) | |

The TLPP rates at 3 and 6 months were 39/41 (95.1%) and 28/39 (71.8%) respectively (Figure 1). Circuit access patency rates at 3 and 6 months were 35/37 (94.6%) and 22/35 (62.9%) respectively (Figure 1). The estimated mean target lesion revascularisation free duration was $5.9 \pm 2.0$ months.

*Subgroup analysis.* Further subgroup analyses were carried out to look at outcome differences between de novo and recurrent lesions and whether the TLR rate was different if the lesion were located around the juxta-anastomosis (JAS) or elsewhere. The TLPP rate was higher albeit

**Table 2.** Procedural details.

| | Number of events | Percentage |
|---|---|---|
| Indication for intervention | ($n=39$) | |
| Dropping access flow | 24 | 61.5 |
| High venous pressure | 5 | 12.8 |
| Cannulation difficulties | 4 | 10.3 |
| Post cannulation bleeding | 4 | 10.3 |
| Others | 2 | 5.1 |
| De novo | 10 | 25.6 |
| Recurrent | 29 | 74.4 |
| Location of target lesion | ($n=43$) | |
| Juxta-anastomotic segment | 24 | 54.5 |
| Distal outflow | 11 | 22.7 |
| Cephalic arch | 5 | 11.4 |
| Cannulation zone | 4 | 9.1 |
| De novo | 14 | 31.8 |
| Recurrent | 29 | 65.9 |
| Mean time from prior intervention, months (SD) | $7.3 \pm 4.0$ | |
| SEB diameter (mm) | ($n=47$) | |
| 7 | 32 | 68.1 |
| 6 | 13 | 27.7 |
| 5 | 1 | 2.1 |
| 4 | 1 | 2.1 |

SEB: sirolimus eluting balloon; Others: high arterial pressure, persistent pain over fistula site.

**Table 3.** Cumulative deaths, abandoned AVFs, and adverse events.

| | Number of events ($n=39$) | Percentage |
|---|---|---|
| Death | | |
| 3-months | 1 (IHD) | 2.6 |
| 6-months | 3 (IHD, MODS, cancer) | 7.7 |
| AVF abandoned | | |
| 3-months | 1 (Haemorrhage) | 2.6 |
| 6-months | 1 (haemorrhage) | 2.6 |
| Adverse events | | |
| Stroke | 0 | 0 |
| Pulmonary embolism | 0 | 0 |
| Allergic reaction | 0 | 0 |

IHD: ischemic heart disease; MODS: multiple organ dysfunction syndrome.

**Table 4.** Patency outcomes.

| | Number of events (%) | *p*-Value |
|---|---|---|
| 3-month patency outcomes | | |
| Target lesion primary patency ($n=41$) | 39 (95.1) | – |
| De novo ($n=14$) | 13 (92.9) | 1.00 |
| Recurrent ($n=27$) | 26 (96.3) | |
| JAS ($n=23$) | 21 (91.3) | 0.50 |
| Non-JAS ($n=18$) | 18 (100) | |
| Circuit access primary patency ($n=37$) | 35 (94.6) | – |
| De novo ($n=10$) | 9 (90.0) | 0.47 |
| Recurrent ($n=27$) | 26 (96.3) | |
| Circuit primary assisted patency ($n=37$) | 37 (100) | – |
| 6-month patency outcomes | | |
| Target lesion primary patency ($n=39$) | 28 (71.8) | – |
| De novo ($n=13$) | 9 (69.2) | 1.00 |
| Recurrent ($n=26$) | 19 (73.1) | |
| JAS ($n=21$) | 15 (71.4) | 1.00 |
| Non-JAS ($n=18$) | 13 (72.2) | |
| Circuit access primary patency ($n=35$) | 22 (62.9) | – |
| De novo ($n=9$) | 7 (77.8) | 0.43 |
| Recurrent ($n=26$) | 15 (57.7) | |
| Reasons for reintervention | | |
| Dropping access flow | 7 | |
| High venous pressure | 3 | |
| Cannulation difficulties | 1 | |
| Thrombosis | 1 | |
| Retrograde flow | 1 | |
| Circuit primary assisted patency ($n=35$) | 33 (94.3) | – |
| Mean time to target lesion reintervention, months ($\pm$SD) | $3.7 \pm 1.2$ | – |
| De novo | $4.5 \pm 1.4$ | 0.20 |
| Recurrent | $3.3 \pm 1.0$ | |
| JAS | $3.4 \pm 1.2$ | 0.28 |
| Non-JAS | $4.1 \pm 1.1$ | |

JAS: juxta-anastomotic segment.

insignificant for the recurrent compared to the de novo lesions at both 3- (96.3% vs 92.9%; $p=1.00$) and 6-months (73.1% vs 69.2%; $p=1.00$). The estimated median TLR-free duration was higher for recurrent versus de novo lesions ($6.7 \pm 1.8$ months vs $7.0 \pm 0.7$; $p=0.43$) but did not reach significance. Figure 2(a) shows Kaplan-Meier estimates for target lesion primary patency for de novo versus recurrent lesions. The estimated mean TLR- free duration in patients with a JAS stenosis ($6.8 \pm 1.3$ months) was not significantly higher than those with non-JAS lesion ($6.7 \pm 1.8$ months; 95% CI: −1.1 to 1.2 months; $p=0.91$). The TLPP rates in patients with a JAS stenosis were lower but were not significantly difference compared with those with a non-JAS stenosis at 3 months (91.3% vs 100%; $p=0.50$) and at 6 months (71.4% vs 72.2%; $p=1.0$). Figure 2(b) shows Kaplan-Meier estimates for target lesion primary patency for JAS versus non-JAS lesions.

## Discussion

*ISABELLA's* main findings demonstrate excellent technical and procedural success rates (100%) using the *Selution SLR*™ SEB, after adequate lesion preparation

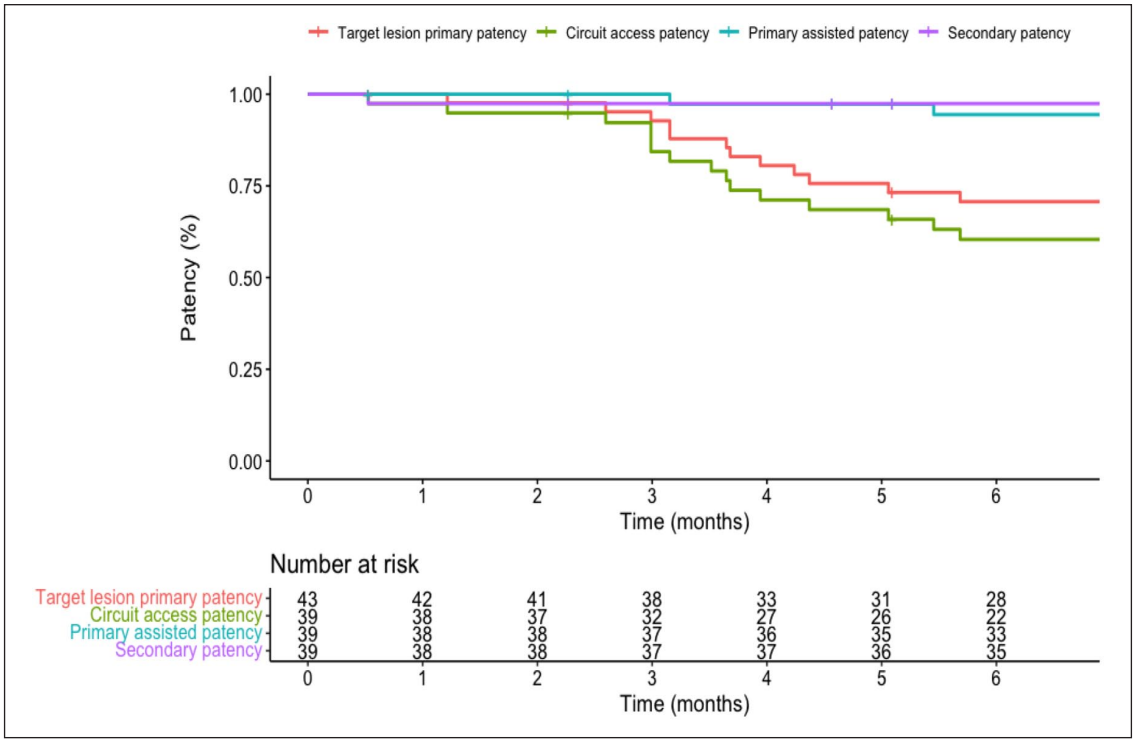


**Figure 1.** Kaplan-Meier estimates for target lesion primary patency, circuit access patency, primary assisted patency, and secondary patency.

with a high pressure non-compliant balloon. Furthermore, it delivered 3- and 6-months TLPP of 95% and 72% respectively and a mean clinical TLR-free duration of 5.9 months. Safety data showed three deaths (7.7%) outside the 30-day window, attributable to the patients' underlying co-morbidities and not to balloon use. One access circuit was lost to overlying AVF skin ulceration (separate site from the access puncture site) and bleeding, which required urgent AVF ligation, 2 weeks after successful endovascular salvage.

The experience using sirolimus-based balloon platforms in the AVF field remains primordial with only a few small pilot clinical studies recently reporting relatively short term outcomes.[17,18,22] The *MAgicTouch*™ Intervention Leap for Dialysis Access (*MATILDA*) single arm prospective pilot trial from our group enrolled 33 ESRF Asian patients with dysfunctional AVF[22] using the *MagicTouch*™ DCB catheter (Concept Medical Inc., Tampa, FL, US), which is the competitor SEB currently available today for the peripheral vasculature. There were 100% technical and procedural success rates and there were no peri-procedural complications related to the SEB – similar to our experience with the *Selution SLR*™. The TLPP and circuit access patency rates at 6 months were 83% and 68% respectively, comparable to the results with *ISABELLA*. The high TLPP rates demonstrated in both studies may also be down to good lesion preparation using a versatile high pressure non-compliant balloon (Mustang®), to optimise sirolimus penetration into the fistula wall. We permitted an invariable 2 min high pressure POBA, prior to performing drug elution – again for a further 120 s – to maximise wall drug transfer. A similar balloon inflation protocol was performed in the Aperto Registry[23] showing excellent 6-month TLPP of 88%, albeit with a PCB device. Antiplatelet agent use may also be a factor in the good outcomes reported. There is reported benefit of oral APA for AVF patency at 6 months[24,25] and we used a dual APA regime for 1 month followed by monotherapy, which is a more aggressive adjuvant medical policy than some of the other recent AVF DCB trials.[26,27] The two largest RCTs to date comparing PCB versus POBA in AVF are worth discussing in this regard. The *Lutonix AV Randomised Trial* was the first prospective, global, multicentre RCT that compared the efficacy and safety of PCB-assisted angioplasty ($n=141$) with POBA ($n=144$) in patients with dysfunctional mature AVFs. The TLPP for the PCB group was 71% compared to 63% for the POBA cohort and although there was a trend for better patency for PCB, the pre-specified 6-month primary efficacy endpoint was not met. Recently, 12-month outcomes of the *IN.PACT AV Access* study ($n=330$) were presented showing an impressive 82.2% and 63.8% TLPP in the PCB arm at 6- and 12 months respectively, compared to 59.5% and 43.6% TLPP in the POBA arm.[28,29] This was the first PCB versus POBA trial to meet its primary effectiveness endpoint and that there was a highly significant advantage in terms of reduced CD-TLR for the PCB treated group. One of the

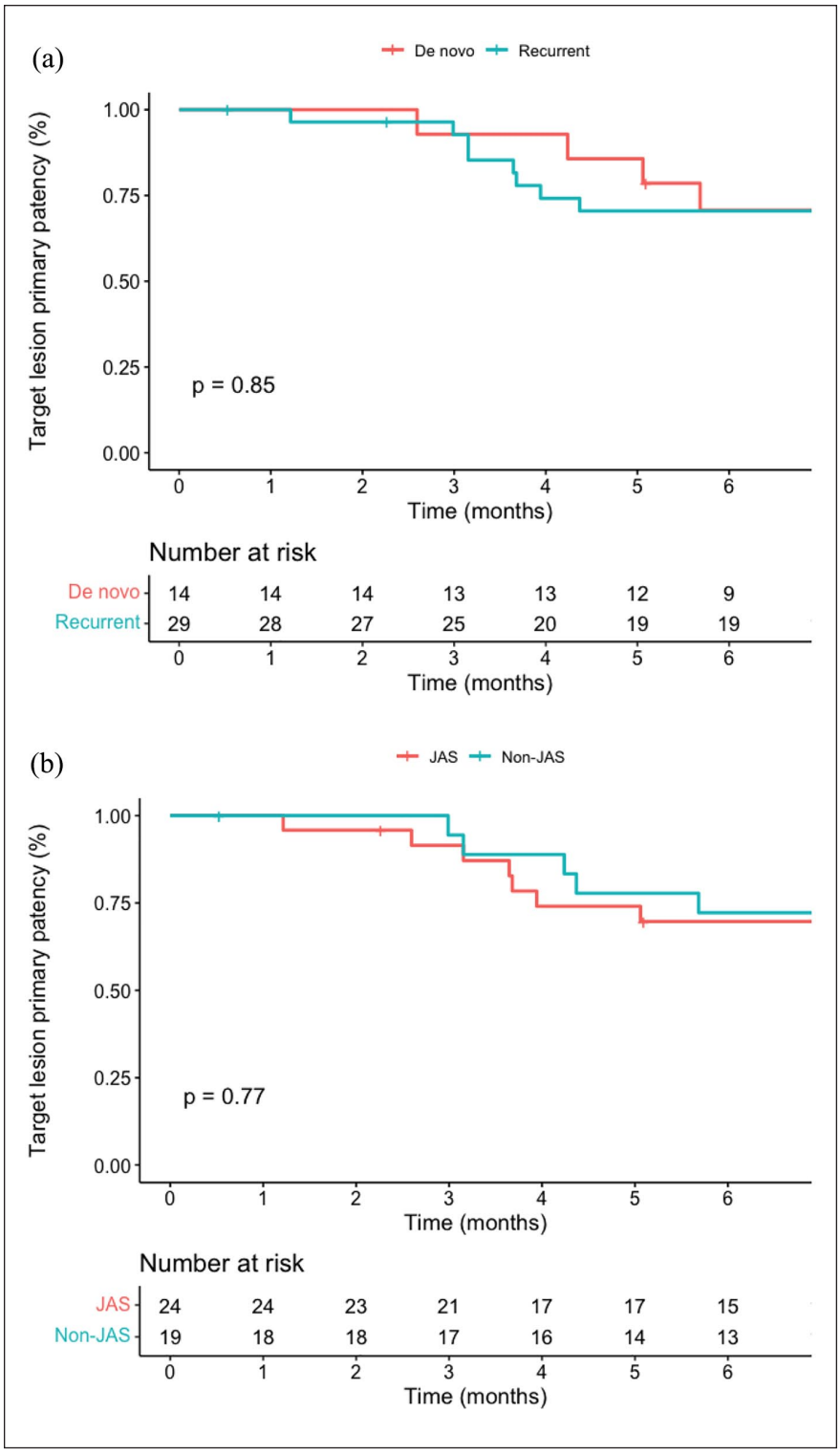


**Figure 2.** Kaplan-Meier estimates for target lesion primary patency across: (a) patency (de novo vs recurrent) and (b) lesion location (juxta-anastomotic, JAS vs non-JAS) sub-groups.

differences between *Lutonix AV* and *IN.PACT AV* was the difference in frequency of APA therapy between the PCB and POBA arms post procedure. The PCB arm in IN.PACT AV had more patients on APA than the CBA arm at both the 3 and 6 months timepoints whereas in *Lutonix AV*, the frequency of APA prescribing was similar between the two groups, which may have influenced the results. However use of APA is one of many variables in RCTs especially in

challenging ESRF patients with multiple co-morbidities and where APA use in HD around the world is still very variable.

We have recently reported 1 year efficacy data from *MATILDA* showing that TLPP and circuit access patency dropped to 58% and 44% respectively.[17] Although disappointing, it may not be of surprise because the current comparative paclitaxel data in AVF is similar (PCB pooled TLPP was 75% and 53% at 6 and 12 months respectively).[30] The Kaplan-Meier curves comparing TLPP difference between POBA and PCB in the AVF circuit tend to converge over time. The paclitaxel load that is delivered to the vessel wall likely differs to some extent between PCBs because of dose, different excipient carriers and amount of drug that is washed downstream during balloon inflation. The decline in TLPP between the 6 and 12 month timeframe in all the PCB studies suggests the need to perform repeated drug elution for drug refuelling into the fistula wall to prolong TLPP. What is encouraging and unique with the *Selution SLR*™ SEB is that it has now published basic science data to demonstrate pharmacokinetic activity and histological animal safety studies to give credence behind its use.[19] There was robust and prolonged arterial tissue retention of sirolimus with therapeutic levels up to 60 days within the vessel wall and blood levels declined rapidly after SEB treatment and were not detected after 7 days. Despite the use of biodegradable PDLA microspheres to deliver sirolimus to the arterial wall over extended periods, there was no evidence of downstream emboli or tissue reaction indicative of adverse particulate effects, which have previously been linked to the use of paclitaxel coated devices[31] and postulated as a mechanism of higher major amputations in the peripheral vasculature.[32] However the use of PCBs in dialysis has not shown any difference in short- to midterm mortality compared with POBA in a recent meta-analysis.[33] The potent antiproliferative and anti-inflammatory properties of sirolimus make it an ideal agent to reduce the risk of restenosis, especially with a drug retention time within the arterial wall of 60 days, which is longer than for paclitaxel (approximately 1 month)[34] and ideal to prolong the anti-restenotic effect in AVFs. We look forward to see if this is borne out with the results of this trial at 1 year.

Liao et al.[35] has previously shown that stenotic lesions may respond differently to DCB, depending on site (JAS vs non-JAS) and whether the lesion is recurrent or de novo. Recurrent lesions usually require more frequent reinterventions. Irani et al.[36] demonstrated that PCB angioplasty offered a greater benefit for recurrent stenoses in more mature AVF circuits but the Aperto Registry showed that the potential for restenosis inhibition by paclitaxel may well be greatest in younger fistulas.[23] The *MATILDA* study showed that recurrent lesions seemed to have a better 3- and 6 month TLPP than de novo lesions, albeit insignificant[22] and there was a trend for a higher TLR-free duration with recurrent lesions in this study too. Data suggest that JAS compared to non-JAS lesions respond better to PCB because the inflammatory response seems to be more pronounced in this region and hence the anti-inflammatory properties of SEB would be an advantage but results from both *MATILDA* and *ISABELLA* are equivocal, perhaps due to limited patient numbers.

### *Limitations*

Limitations of this study include its small sample size, non-randomised, non-consecutive, single arm nature and self-adjudication without independent core lab verification, albeit adding novel data to the existing literature on AVF DCB endovascular salvage. However the patient recruitment was fast, broad-based with few exclusion criteria, reflecting a real-life everyday registry of Asian ESRF patients presenting with AVF dysfunction requiring fistuloplasty. The lack of a comparator group precludes any statement on patency rates in this population using alternative interventions such as PCB and POBA. Furthermore, use of a high pressure non-compliant balloon to prepare the lesion prior to SEB is also a limitation because prior POBA AVF data used semi-compliant balloons and although there is no evidence to suggest high pressure non-compliant balloons are more effective than conventional balloons, this does raise the question whether part of the efficacy seen in ISABELLA is from the lesion preparation itself. This would also be a limitation on the sample size calculation and perhaps aid in a Type II error. A 6-month follow-up period is probably too short to provide conclusive data for safety and efficacy over a timeframe relevant to HD patient care. As highlighted, a major consideration with PCBs has been the slight increase in mortality with these agents when used to lower limb lesions. Although you cannot be certain that SEB does not confer a higher mortality than expected from this study (7.7%), this is tempered by the fact that 1-year mortality rates for haemodialysis patients between 2014 and 2018 was higher from the Singapore Renal Registry (nrdo.gov.sg), approximately 9.7%. A strength of this pilot study is the prospective nature and completeness of patient follow-up and the data can be confidently used to help power any future RCT looking at SEB versus CBA. Although the therapeutic effect of combined high pressure POBA and SEB angioplasty looks promising, cost-effectiveness calculations need to be performed as well in any future RCT, as it is likely to be an expensive undertaking.

## Conclusion

Fistuloplasty using the novel *Selution SLR*™ SEB for failing AVFs seems a safe and effective modality in Asian haemodialysis patients at 6 months but larger randomised controlled studies are required now to determine its true

efficacy against plain balloon angioplasty and these RCTs should look at superiority and not non-inferiority of SEB versus POBA.

## Author contributions

TYT was primarily involved in study design, protocol development, implementation and analysis of the data at study site, as well as patient recruitment. CST, RYT, SCP, AP, AG and TTC were involved in patient recruitment and edited the final draft of the manuscript. CJQY, SXYS coordinated the project and patient communication and were involved in manuscript preparation with TYT. SXYS aided with the data analysis and statistical prowess. All authors have read and approved the final manuscript.

## Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: TYT and TTC have received physician-initiated study grants and honoraria for speaking engagements from M.A. MedAlliance SA.

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## ORCID iDs

Tjun Y Tang https://orcid.org/0000-0002-8524-7912
Shereen XY Soon https://orcid.org/0000-0003-3057-5983
Charyl JQ Yap https://orcid.org/0000-0002-8606-0842
Ru Yu Tan https://orcid.org/0000-0003-1491-2302
Chieh Suai Tan https://orcid.org/0000-0002-8850-5585

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