Single-Center Prospective Pilot Study of Sirolimus Drug-Coated Balloon Angioplasty in Maintaining the Patency of Thrombosed Arteriovenous Graft

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ABSTRACT

Purpose: To investigate the use of a sirolimus drug-coated balloon (DCB) in the management of a thrombosed arteriovenous graft (AVG).

Materials and Methods: A single-center prospective pilot study was conducted between October 2018 and October 2019. Twenty patients (age = 67.0 years ± 10; male = 35%; mean time on dialysis = 31 months) with thrombosed upper limb AVG were enrolled. After successful pharmacomechanical thrombectomy and adequate treatment of the graft vein junction, sirolimus DCB angioplasty was performed at the graft vein junction. The patients were followed-up for 6 months, and all adverse events occurring during the study period were recorded.

Results: The primary circuit patency rates at 3 and 6 months were 76% and 65%, respectively, while the assisted-primary circuit patency rates at 3 and 6 months were 82% and 65%, respectively. The 3- and 6-month secondary circuit patency rates were 88% and 76%, respectively. Using Kaplan-Meier analyses, the estimated mean primary, assisted-primary, and secondary patencies were 285 days (95% confidence interval (CI) = 194–376 days), 319 days (95% CI = 221–416 days), and 409 days (95% CI = 333–485 days). No adverse event directly related to sirolimus DCB use was observed.

Conclusions: The results of this pilot study suggest that the application of sirolimus DCB at the graft vein junction after the successful thrombectomy of AVG may be a feasible option to improve patency outcomes.

ABBREVIATIONS

AVG = arteriovenous graft, CI = confidence interval, DCB = drug-coated balloon, PBA = plain balloon angioplasty, RCT = randomized controlled trial

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Due to suboptimal patency rates of arteriovenous graft (AVG) following percutaneous interventions, specialized balloons and implants have been tested in clinical trials to improve the durability of AVGs and reduce reintervention rates. The therapeutic efficacy of the stent graft in the treatment of graft vein junction stenosis has been convincingly demonstrated in several randomized controlled trials (RCTs) (1–4). Although the use of stent graft could prevent elastic recoil and change flow dynamics to the graft vein junction, it could impede future surgical revision or creation of a secondary arteriovenous fistula in the ipsilateral arm and might not be suitable for all patients. Moreover, in a thrombosed AVG, despite the superiority of stent graft over plain balloon angioplasty (PBA), the 6-month primary target lesion and circuit patency remained at 34% and 36%, respectively (3).

Several recent RCTs have demonstrated superiority of a paclitaxel drug-coated balloon (DCB) over PBA in dialysis access interventions (5–8). However, patients with AVG were excluded from 2 of 5 RCTs. Specifically, patients with thrombosed AVGs were excluded from all the RCTs. Although the use of paclitaxel DCB at the graft vein junction has been shown in 1 of the RCTs to improve the absolute target lesion and circuit primary patency at 6 months by 32% and 27%, respectively, in nonthrombosed AVG (9), a separate retrospective analysis of the use of paclitaxel DCB in patients with thrombosed AVG showed that they continued to fare poorly, with 6-month circuit patency rates of only 23% (10). Hence, there is much potential for improvement in the patency rate of thrombosed AVG after successful thrombectomy.

Sirolimus DCB is a second-generation DCB that has been successfully used in coronary artery interventions to prevent restenosis (11,12). The effect of sirolimus DCB in hemodialysis arteriovenous access interventions has not been previously investigated. In this study, it was hypothesized that in thrombosed AVG, sirolimus DCB angioplasty of the graft vein junction following successful pharmacomechanical thrombectomy and adequate graft vein junction treatment would improve its patency by inhibiting neointimal hyperplasia. Patients with thrombosed AVGs were recruited as they have the worst patency outcome among patients presenting with dysfunctional arteriovenous access and represent an unmet need in clinical practice. Hence, this investigator-initiated pilot study was conducted to examine the feasibility of using sirolimus DCB at the graft vein junction following successful pharmacomechanical thrombectomy of a thrombosed AVG.

MATERIALS AND METHODS

Study Design

This single-center, prospective, phase 2 study was investigator-initiated and carried out in accordance with ethical principles that have their origins in the Declaration of Helsinki. The study was registered with ClinicalTrials.gov and was approved by the institution's centralized institutional review board. Informed consent was obtained from all recruited subjects. A detailed description of the protocol, including study design, rationale, sample size calculations, patient selections, investigational device, study procedure, efficacy, and safety endpoints, was previously published (13). In brief, patients admitted with thrombosed AVGs were screened for eligibility, with a recruitment target of 20 patients over a 1-year period. Following successful pharmacomechanical thrombectomy (using a combination of a thrombolytic agent, balloon angioplasty, and Fogarty embolectomy balloon catheter) and adequate treatment of the graft vein junction (defined as <30% residual stenosis compared to a healthy segment of the AVG) with either high pressure or cutting balloons, sirolimus DCB (MagicTouch, Concept Medical, India) was administered to the graft vein junction. The concentration of sirolimus on the balloon was 1.27 μg/mm^2. The diameters of the DCB used in this study were 7 and 8 mm, with a balloon length of 8 cm and shaft length of 80 cm over a 0.035-inch wire. Dual antiplatelet therapy with aspirin (100 mg) and clopidogrel (75 mg) once a day was prescribed for 1 month after the angioplasty. This was in accordance with the instruction for use of sirolimus DCB in coronary artery interventions.

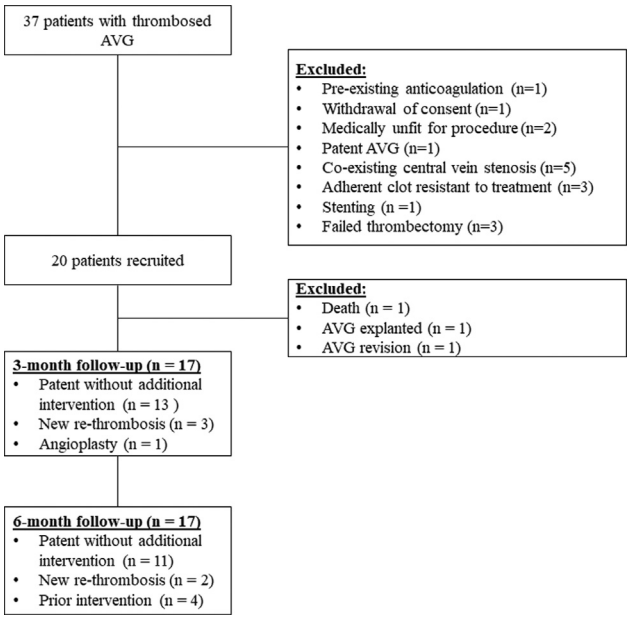

Figure 1. Study population.

All the participants were assessed via a telephone call at 1 month for localized infection, hematoma, or bleeding of the AVG; compliance with the antiplatelet therapy; and identification of any adverse effects from the antiplatelet therapy and DCB angioplasty. All the patients were followed-up at 3 and 6 months as outpatients, with clinical and ultrasound evaluations of their graft to assess for circuit patency and freedom from any local and systemic adverse reactions.

The patency outcomes were classified according to the recommendations by the Society of Interventional

Table 1. Baseline Demographics of the Study Population

Demographics, n = 20	Number (%) or mean ± SD
Age, y	67.0 ± 10
Gender, n (%) male	7 (35)
Ethnicity, n (%)	
Chinese	15 (75)
Malay	4 (20)
Indian	1 (5)
Time on dialysis, mo*	31 (11, 88)
Etiology of end-stage renal disease	
Diabetes	7 (35)
Hypertension	4 (20)
Chronic glomerulonephritis	8 (40)
Polycystic kidney disease	1 (5)
Vintage of AVG, mo*	14 (12, 20)
Site of AVG	
Upper arm	18 (90)
Forearm	2 (10)
Types of AVG	
Brachiobasillic	3 (15)
Brachioaxillary	15 (75)
Brachiobrachial	1 (5)
Radiobasillic	1 (5)
AVG configuration	
Straight	17 (85)
Loop	3 (15)
Diameter of AVG at venous anastomosis	
6 mm	16 (80)
7 mm	4 (20)
Number of previous interventions	
0	12 (60)
1–2	4 (20)
3–4	1 (5)
More than 4	3 (15)
Number of antiplatelet agents	
0	9 (45)
1	9 (45)
2	2 (10)

AVG = arteriovenous graft; mo = months; SD = standard deviation; y = years.
*Results are reported as median (25th, 75th percentile)

Radiology (14). Primary patency after the intervention was defined as the interval between the intervention and next required intervention (angioplasty, thrombolysis, or surgical revision). Assisted-primary patency after the intervention was defined as the interval between the intervention and subsequent access thrombosis, while secondary patency was defined as the interval between the intervention and when the access was abandoned. Reinterventions were performed when there were difficulties with cannulation, prolonged bleeding after needle removal, abnormal dialysis circuit alarms, unexplained decreases in dialysis clearance, or thrombosis of the access.

Study Participants

Between October 1, 2018, and October 2, 2019, 65 unique patients were admitted with thrombosed AVG to the institution. A total of 37 patients who fulfilled the initial eligibility criteria were enrolled, and 20 patients were recruited. The reasons for exclusion of 17 patients are summarized in Figure 1. Ten different operators (median years of experience = 8.5 years, range = 3–22 years) in the institution performed the procedures. The first patient was recruited on October 23, 2018. The last patient completed follow-up on March 2, 2020. All the recruited participants were included in the statistical analysis.

The demographic data of the 20 patients recruited for the study are summarized in Table 1. Majority of the AVGs were located in the upper arm in either a brachioaxillary or brachiobasilic configuration. Eleven patients were on pre-existing antiplatelet therapy. The procedural details of the pharmacomechanical thrombectomy for each patient are shown in Table 2. Recombinant tissue plasminogen activator (2–4 mg) was used in 65% of the cases (n = 13), while urokinase (120,000–180,000 units) was used in the remaining patients. Embolectomy catheters were used in 19 patients to trawl the arterial plug. No thrombectomy device was used. Four patients required a cutting balloon to treat the graft vein junction adequately before DCB angioplasty. DCBs of 7-mm diameter were used in 13 patients, while DCBs with diameters of 8 mm were used in the remaining 7 patients. No immediate procedural complications were recorded during the thrombectomy or use of sirolimus DCBs.

Statistical Analysis

Continuous variables were summarized as mean ± standard deviations for normally distributed variables or median and interquartile ranges (25th percentile, 75th percentile) for non-normally distributed variables, while categorical variables were reported using frequency counts and percentages. The primary, assisted-primary, and secondary patency rates were reported for both "intention-to-treat" and "per-protocol" analyses. Kaplan-Meier survival analyses were used to examine the primary, assisted-primary, and secondary patency rates of the AVGs. The data analyses were performed with STATA (StataCorp 2019, Stata Statistical Software Release 16, StataCorp LLC, College Station, Texas) and SPSS version 23 (IBM Corp, Armonk, New York).

RESULTS

Efficacy and Safety

Primary Endpoint. At 3 months, using the per-protocol analysis (n = 17), the circuit primary patency rate was 76%, while the target lesion primary patency was 82% (Table 3). After including 3 patients who did not complete at least 3 months of follow-up in the intention-to-treat

Table 2. Characteristics of Endovascular Thrombectomy

Case	AVG Age, mo	Number of Previous Thrombosis in 12 mo	Thrombolytic Agent (Dose)	Preparation Balloons		DCB	3-mo Follow-Up		6-mo Follow-Up	
				Size, mm	Type	Size, mm	Outcome	Access Flow, mL/min	Outcome	Access Flow, mL/min
1	13	0	rtPA (4 mg)	7	Cutting balloon	8	Patent	440	Re-thrombosis at day-193	NA
2	12	0	rtPA (4 mg)	7	High pressure	7	Surgical revision of cannulation segment for bleeding pseudoaneurysm at day-8	NA	NA	NA
3	102	0	rtPA (4 mg)	8	High pressure	8	Patent	790	Patent	430
4	19	5	Urokinase (180,000 unit)	7	High pressure	7	Angioplasty of intragraft stenosis at day-74	NA	NA	NA
5	20	0	Urokinase (180,000 unit)	7	Cutting balloon	7	Patent	660	Patent	650
6	4	0	rtPA (4 mg)	6	High pressure	7	Death at day-40	NA	NA	NA
7	13	2	rtPA (4 mg)	7	High pressure	7	Patent	640	Re-thrombosis at day-157	NA
8	12	0	Urokinase (180,000 unit)	8	High pressure	7	AVG explanted for infection at day-88	NA	NA	NA
9	15	0	Urokinase (180,000 unit)	6	Cutting balloon	7	Patent	250	Re-thrombosis at day-134	NA
10	32	2	rtPA (3 mg)	7	High pressure	7	Re-thrombosis at day-56	NA	3 interventions in 6-months	NA
11	10	0	rtPA (4 mg)	7	High pressure	7	Re-thrombosis at day-14	NA	NA	NA
12	12	1	Urokinase (180,000 unit)	7	High pressure	7	Patent	800	Patent	450
13	36	0	rtPA (4 mg)	7	High pressure	8	Patent	820	Patent	620
14	13	0	rtPA (4 mg)	7	High pressure	8	Patent	2440	Patent	2110
15	25	1	Urokinase (180,000 unit)	7	High pressure	8	Patent	760	Patent	1060
16	18	0	rtPA (4 mg)	7	High pressure	8	Patent	770	Patent	570
17	17	2	rtPA (4 mg)	7	High pressure	7	Patent	940	Patent	1490
18	119	0	rtPA (2 mg)	7	High pressure	8	Patent	660	Patent	520
19	4	0	rtPA (4 mg)	6	Cutting balloon	7	Re-thrombosis at day-32	NA	3 interventions in 6-months	NA
20	19	0	Urokinase (120,000 unit)	7	High pressure	7	Patent	630	Patent	1840

AVG = arteriovenous graft , DCB = drug-coated balloon, rtPA = recombinant tissue plasminogen activator, AVG = arterio venous graft, NA = not applicable.

analysis (n = 20), the circuit and target lesion primary patency rates were 65% and 70%, respectively.

Of the 3 patients who did not complete the 3-month follow-up due to adverse events, 1 patient required a surgical revision of the "arterial" limb of the AVG due to a bleeding pseudoaneurysm at the puncture site 8 days after the intervention. The treated graft vein junction was patent, and only the arterial limb of the graft was revised. Another patient died due to an acute intracranial hemorrhage 40 days after the intervention. He was on single antiplatelet therapy at the time of the intracranial hemorrhage. The last patient required an explant of the AVG due to a graft infection at 88 days after the intervention. Significantly, all the AVGs were patent and functioning well at the time of the event, and these events were assessed to be unrelated to the DCB angioplasty.

Rethrombosis of the AVGs occurred in 3 patients at 14, 32, and 56 days after the intervention. Repeat thrombectomy was performed in these 3 patients. Pullback venograms of these 3 patients showed that the grafts were thrombosed up to the graft vein junction. Another patient who lost circuit primary patency underwent an elective angioplasty performed for low access flow rate with abnormal dialysis circuit pressure at 76 days after the recruitment. The low flow rate was due to intragraft stenosis, and the graft vein junction was patent during the procedure.

Secondary Endpoints. In the per-protocol analysis, the 6-month primary circuit patency rate was 65%, as shown in Table 3. Two patients had rethrombosis of the AVG at 135 and 157 days after the intervention. Repeat thrombectomy was performed in these 2 patients. Pullback venograms of these 2 patients showed that the grafts were thrombosed up to the graft vein junction. Overall, the 3- and 6-month assisted-primary patency rates were 82% and 65%, while the secondary patency rates were 88% and

Table 3. Primary and Secondary Outcomes

Outcomes, n (%) or mean (standard deviation)	Intention-to-treat analysis n = 20	Per-protocol analysis n = 17
Primary outcomes		
Primary patency at 3 mo	13 (65)	13 (76)
Secondary outcomes		
Primary patency at 6 mo	11 (55)	11 (65)
Assisted-primary patency at 3 mo	14 (70)	14 (82)
Assisted-primary patency at 6 mo	11 (55)	11 (65)
Secondary patency at 3 mo	16 (80)	15 (88)
Secondary patency at 6 mo	14 (70)	13 (76)
Number of interventions to maintain patency at 6 mo		
0		11 (65)
1		4 (24)
>2		2 (12)
Intra-access flow, mL/min		
3 mo		820 ± 520
6 mo		970 ± 620

77%, respectively. With the intention-to-treat analysis, the 6-month primary circuit patency rate was 55%. The 3- and 6-month assisted-primary patency rates were 70% and 50%, respectively, while the secondary patency rates were 80% and 70%, respectively (Table 3).

Four patients required 1 intervention, and 2 patients required more than 2 interventions during the 6-month follow-up to maintain patency of the AVGs (Table 2). The mean intra-access flow volume was 820 mL/min ± 520 and 970 mL/min ± 620 at 3 and 6 months, respectively. Using the Kaplan-Meier analysis, the estimated mean primary, assisted-primary, and secondary patencies were 285 days (95% confidence interval [CI] = 194–376 days), 319 days (95% CI = 221–416 days), and 409 days (95% CI = 333–485 days) (Fig 2).

Safety Endpoints. No adverse events directly related to DCB use or pharmacomechanical thrombectomy were reported. Five serious adverse events were recorded during the follow-up but were all considered unrelated to the procedure or DCB. The 5 circumstances were (*a*) a bleeding pseudoaneurysm, (*b*) an intracranial hemorrhage, (*c*) a graft infection, (*d*) a mechanical fall, which was complicated by a distal radial fracture of the AVG arm, and (*e*) hospitalization for treatment of a diabetic foot ulcer. There was no report of bleeding episodes while the patients were on dual antiplatelet therapy.

DISCUSSION

Although pharmacomechanical thrombectomy of a thrombosed AVG is associated with a high technical success rate, its long-term patency remains poor, and repeated interventions are often required to maintain its patency (10,14). The average reported rates of 3- and 6-month primary patency for management with pharmacologic thrombolysis or mechanical thrombectomy are only 49% and 38%, respectively (14). A review of devices studied in RCTs to improve patency rates of nonthrombosed and thrombosed AVGs is summarized in Table 4 (1–3,15,16). In the landmark FLAIR pivotal study, Haskal et al (1) demonstrated superiority in patency rates at 6 months with the use of a stent graft compared to those with the use of PBA in patients with graft vein junction stenosis. The subsequent RENOVA study demonstrated similar superiority of a stent graft over PBA at 6 months, and the superiority persisted at 12 months (2). In the REVISE trial (3), which included patients with both thrombosed and nonthrombosed AVGs, the use of stent graft was again shown to be statistically superior to PBA at 6 months for target lesion patency in an intention-to-treat analysis, with circuit patency rates of 34.2% with the use of covered stents after successful thrombectomy.

The present study demonstrated that the application of sirolimus DCB at the graft vein junction after successful pharmacomechanical thrombectomy of thrombosed AVG (n = 17) results in 3- and 6-month circuit patencies of 76% and 65%, respectively. After including the 3 patients who did not complete at least 3 months of follow-up in the intention-to-treat analysis (n = 20), the 3- and 6-month patency rates were 65% and 55%, respectively. These patency rates were higher than the threshold of 44% and 31% recommended by the Society of Interventional Radiology (14).

Sirolimus is a macrocyclic lactone antibiotic with immunosuppressive and antiproliferative properties. It was approved for use alone or with calcineurin inhibitors or corticosteroids in the United States in 1999 to prevent organ rejection after renal transplantation. It has also been approved as a therapy option for lymphangioleiomyomatosis (17). As an immunosuppressant, sirolimus is available as a tablet in doses of 0.5, 1, and 2 mg. After a loading dose, the usual maintenance dose for adults is 2 mg once a day as an immunosuppressant. In comparison, sirolimus is coated on DCB at a concentration of 1.27 μg/mm^2, which would translate to a delivered dose of 2.55 mg for an 8 mm × 8 cm balloon. The delivery of sirolimus from an angioplasty balloon requires the use of a cosolvent or phospholipid nanocarriers for the drug to be delivered to the vessel wall at sustained therapeutic levels (18). Preclinical studies have demonstrated the successful delivery of sirolimus into the tunica medial layer, with some drugs extending into the adventitia (19). The DCB used in this study uses a unique phospholipid coating technology to allow for 100% sirolimus submicron drug particle coating on the balloon surface to facilitate controlled drug delivery into the vessel wall when the balloon is inflated (20).

Compared to paclitaxel, which is cytotoxic, sirolimus is cytostatic and inhibits cell cycle in the G1 phase by inhibiting the mammalian target of rapamycin instead.

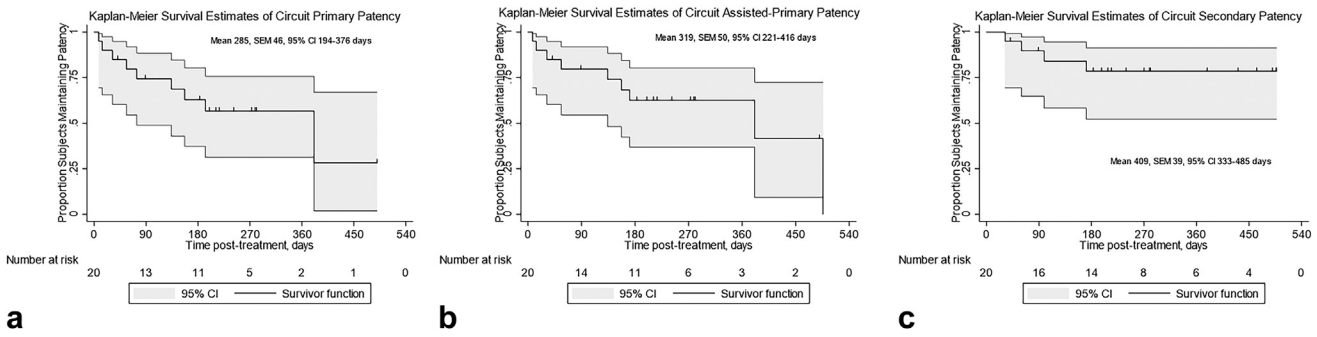

Figure 2. Kaplan-Meier survival curves of the circuit.
(**a**) Primary patency
(**b**) Assisted-primary patency
(**c**) Secondary patency

Table 4. Review of 6-Month Patency Rates of Endovascular Intervention of Nonthrombosed and Thrombosed Arteriovenous Grafts with Different Devices

Author, y	Study design	Device	Number of AVGs	6-mo target lesion patency	6-mo circuit patency
Nonthrombosed					
Vesely, 2005 (15)	Prospective, multicenter RCT	Cutting balloon	340 (nonthrombosed = 195)	PBA: 46.9 % Cutting balloon: 51.3% $P = .844$	PBA: 40.9 % Cutting balloon: 47.3% $P = .756$
Haskal, 2010 (1)	Prospective, multicenter RCT	Stent graft	190	PBA: 23% Stent graft: 51% $P < .001$	PBA: 20% Stent graft: 38% $P = .008$
Saleh, 2014 (16)	Prospective, multicenter RCT	Cutting balloon	295	Graft vein junction PBA: 56% Cutting balloon: 86% $P = .037$ Intragraft PBA: 75% Cutting balloon: 67% $P = .371$	Not reported
Haskal, 2016 (2)	Prospective, multicenter RCT	Stent graft	270	12-mo patency: PBA: 24.8% Stent graft: 47.6% $P < .001$	12-mo patency: PBA: 11% Stent graft: 24% $P < .007$
Vesely, 2016 (3)	Prospective, multicenter RCT	Stent graft	293 (nonthrombosed = 164)	PBA: 45.8% Stent graft: 64.6%	PBA: 35.9% Stent graft: 49.7%
Liao, 2019 (9)	Prospective, single-center RCT	Paclitaxel DCB	44	PBA: 9% PCB: 41% $P = .006$	PBA: 9% PCB: 36% $P = .013$
Thrombosed					
Vesely, 2005 (15)	Prospective, multicenter RCT	Cutting balloon	340 (thrombosed = 145)	PBA: 32% Cutting balloon: 43.1% $P = .150$	PBA: 29.3% Cutting balloon: 37.5% $P = .237$
Vesely, 2016 (3)	Prospective, multicenter RCT	Stent graft	293 (thrombosed = 129)	PBA: 23.5% Stent graft: 36.1%	PBA: 21.8% Stent graft: 34.2%

AVG = arteriovenous graft; DCB = drug-coated balloon; mo = months; PBA = plain balloon angioplasty; RCT = randomized controlled trial; y = years.

The risk of systemic toxicity is low as the absolute dose of sirolimus used in DCB is much lower compared to its regular dose as an immunosuppressive agent in renal transplant recipients. The transfer of sirolimus from the balloon to the systemic circulation during drug delivery via DCB angioplasty is also minimal (21). In this study, no adverse reaction directly related to DCB use was observed. The adverse events that occurred during the

study period were unrelated to the endovascular procedure or sirolimus DCB.

There were several important limitations of this study. This was a single-center study with a small sample size that limited its power and generalizability. There may also have been a selection bias as only patients without no residual stenosis or thrombus after successful thrombectomy were treated with DCB. The use of a cutting balloon to treat elastic recoil in some patients may have confounded the final results as cutting balloon has been shown to statistically improve the 6-month assisted-primary patency of stenotic graft vein junction in a subgroup analysis of an RCT comparing cutting balloons and conventional balloons (86% vs 56%) (16). However, in an RCT that included a thrombosed AVG, the use of a cutting balloon has been shown to provide an equivalent 6-month patency when compared to standard PBA (37.5% vs 29.3%) (15). Nevertheless, the requirement for a cutting balloon in some of the patients has demonstrated the need to treat acute elastic recoils, which are often seen during the treatment of graft vein junction stenosis. This is crucial as the primary purpose of sirolimus is to retard neointimal hyperplasia and not elastic recoil. Hence, it is important to ensure that acute recoil is adequately treated to achieve an optimal luminal vessel diameter with either high pressure or a cutting balloon before the application of DCB to attain the goal of maintaining the luminal diameter through retardation of neointimal hyperplasia. In addition, there was no control group to directly compare the benefits of DCB over plain balloon in thrombosed AVGs, and a comparison with historical data using other devices, such as a covered stent, would be difficult. Of note, the treatment of graft vein junction with stent grafts was convincingly superior to PBA in 3 large RCTs and should serve as the gold standard therapy for subsequent studies on AVG. Nevertheless, within the limits of this study, the findings suggested that the application of sirolimus DCB at the graft vein junction after the successful thrombectomy of an AVG may be feasible and might serve as a viable alternative to currently available devices.

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