Drug Eluting Stents in Infrapopliteal Arterial Disease: A Pilot Safety Study in an Asian Population

Dear Editor,

Critical limb ischaemia (CLI) is the most severe and advanced form of peripheral arterial disease with high risk of limb loss. Almost one-third of patients undergo major amputation and one-fourth die within the first year of diagnosis.[1] Surgical re-vascularisation can reduce the number of amputations, but is often not feasible, due to the lack of suitable target and conduit vessels and comorbidities.[2]

Currently, percutaneous transluminal balloon angioplasty (PTA) is the preferred option for revascularisation of the below the knee (BTK) arterial lesions. PTA has a high technical success rate (88% to 89%),[3,4] but the long-term results are disappointing with re-stenosis rates reported to be as high as 69% at 3 months.[5]

Randomised controlled studies, as well as meta-analyses, have shown superior patency rates and clinical outcomes of drug eluting stents (DES) compared to PTA and bare metal stents (BMS), in the BTK arteries in the Western population.[6-9] However, there is no published data on the safety of DES in BTK arteries in an Asian population. This pilot study was conducted to address the safety issues and assess the short-term outcomes of this technique.

Materials and Methods

Study Design

The study was an investigator-initiated prospective single arm open-label trial. Institutional review board approval was obtained and all recruited patients gave written informed consent to participate in the study. Patients suffering from CLI (Rutherford 4,5,6) with a single arterial lesion with a length of ≤5 cm or 2 lesions with a length of ≤3 cm each within a BTK (anterior tibial, posterior tibial or peroneal) artery with expected unobstructed runoff to ankle level after treatment were eligible for the study. Iliac disease was excluded on prior Doppler ultrasound. The shorter lesion length chosen for the study was limited by the currently commercially available DES stents.[6] The entire list of inclusion and exclusion criteria is listed in Table 1.

Interventional Technique

Ipsilateral antegrade femoral access was used in all the patients, and arteriograms were performed from the common femoral artery to the pedal arch. Any femoropopliteal lesion was treated with angioplasty at the same sitting. The target lesion was imaged in 2 orthogonal planes. A total of 2000 IU of heparin was administered intra-arterially during the procedure. After successful crossing, appropriately sized DES was deployed after predilatation with a conventional balloon. We used the XIENCE V PRIME™ (Abbott, USA) stents in this study, whose safety and efficacy had been established in the Western population.[6] The procedure was defined as technically successful if the length of the target lesion was covered by the DES with a residual stenosis <20%.

Follow-up

Immediately post-procedure, the patients were commenced on clopidogrel 75 mg daily for at least 6 months and aspirin 100 mg daily for 12 months. The patients were evaluated prior to hospital discharge, and at 1, 3 and 6 months post-procedure. Earlier assessment was performed, if clinically warranted. Clinical follow-up included assessment of the Rutherford score and the ischaemic skin/ulcer changes. Duplex imaging and angiography of the treated limb was performed at the time of discharge and at 6 months post-intervention.

Endpoints

Primary endpoints for the study were primary patency of the treated lesions at 6 months after intervention on angiography. The secondary endpoints were limb salvage rate at 6 month and peri-procedural complications.

Definitions

Primary patency was defined as <50% stenosis within the stented lesion on angiography, without re-intervention in the interim. Limb salvage was defined as freedom from any major amputation at or above the ankle of the treated limb. Minor amputation was defined as amputation below the level of the ankle joint. Acute in-stent thrombosis was defined as occlusion of the stent occurring within 30 days of the intervention, late in-stent thrombosis as one which occurred anytime later than 30 days post-intervention.

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Written informed consent	• Acute limb ischaemia
• If female patient with child-bearing potential, patient may not be pregnant at the study entry and must utilise reliable birth control for the duration of her participation into the study	• Subacute limb ischaemia which requires thrombolysis as initial treatment
• Patient is willing and able to comply with the specified follow-up evaluation	• Previous major amputation of the affected limb (at or above the level of the ankle)
• Critical limb ischaemia, this is Fontaine stage III (ischaemic rest pain) and IV (ischaemic ulcers or gangrene) or Rutherford category 4 (ischaemic rest pain), 5 (minor tissue loss) or 6 (major tissue loss)	• Concurrent iliac or femoropopliteal artery disease not suitable for endovascular or surgical revascularisation
• Stenosis (>50% luminal loss) or occlusion of infragenicular arteries (defined as: distal to the level of the popliteal artery), including the tibiofibular trunk, the anterior tibial artery, the posterior tibial artery and the peroneal artery	• Patients without (expected) distal runoff to the index site
• Infragenicular arterial lesions with a total length of ≤5 cm or 2 infragenicular lesions with a total length of ≤3 cm	• Revascularisation involving the same site within 30 days prior to the index procedure or planned revascularisation of the same limb within 30 days of the index procedure
• At least 1 crural (anterior tibial, posterior tibial or peroneal) artery with expected unobstructed runoff to ankle level after treatment	• Previous implanted stent at the index site
	• Life expectancy of less than 6 months
	• Factors making clinical follow-up very difficult or impossible
	• Known allergy to acetylsalicylic acid (aspirin), clopidogrel, heparin or paclitaxel
	• Known allergy to contrast media
	• Known heparin-induced thrombocytopaenia (HIT type 2)
	• Patient unable or unwilling to tolerate anticoagulant, antiplatelet therapy or contrast media
	• Creatinine clearance <30 mL/min (as derived from the MDRD formula) unless patient is on dialysis
	• PT/PTT of >1.5 times the median of normal that can not be corrected for the time of the procedure
	• INR >1.6 that cannot be corrected for the time of the procedure
	• Thrombocytopaenia of <50,000 which cannot be corrected for the time of the procedure

INR: International Normalised Ratio; MDRD: Modification of Diet in Renal Disease; PT: Prothrombin time; PTT: Partial thromboplastin time

Results

Study Group Demographics

Between July 2012 and December 2013,[10] CLI patients were enrolled into the study. The demographics of the study population and the comorbidities are summarised in Table 2.

Lesion and Procedural Characteristics

The lesion characteristics and the procedural details are listed in Table 3. The mean lesion length was 23.5 mm (range, 15mm to 45 mm) and the majority of the patients had severe stenosis (mean severity of stenosis: 81%, range, 52% to 99%). Nine of the patients had 1 stent deployed. One patient had 2 stents placed due to a lesion length of 45 mm. The technical success rate was 100%.

Table 2. Patient Demographics

	Patient Characteristics
Age	66 +/- 8 years
Male	8 (80%)
Right leg	6/10
Type 2 diabetes	10/10 (100%)
End-stage renal failure	5/10 (50%)
Hypertension	10/10 (100%)
Hyperlipidaemia	8/10 (80%)
Coronary artery disease	5/10 (50%)
History of smoking	5/10 (50%)
Ex-smokers	4
Current	1
Rutherford class	
4	0
5	10
6	0

Table 3. Procedural Characteristics and Follow-up

Patient ID	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Lesion Location	Distal Left ATA	Proximal Right ATA	Proximal Right ATA	Proximal Right ATA	Proximal Left ATA	Proximal Left ATA	Distal Right ATA	Distal Right ATA	Proximal Right PTA	Proximal Right ATA
Lesion severity (mean: 81%)	74%	99%	80%	80%	80%	52%	90%	61%	95%	100%
Lesion length (mean: 23.5 mm)	22	15	28	25	15	18	22	25	20	45
Stent length (mean: 35.3 mm)	28	38	38	38	28	28	28	33	28	28, 38
Stent diameter (mean: 3 mm)	3	3	3	2.5	3	3.5	3	3	3	3, 3
Balloon diameter (mm)	3	3	3	2.5	3	3.5	3	3	3	3
Rutherford score (0-5)										
At-discharge	5	Pt expired	5	5	5	5	5	5	5	5
1 month	5	Pt expired	Missed follow-up	5	5	5	5	5	5	Withdrew
3 months	4	Pt expired	1	5	5	5	4	5	5	Withdrew
6 months	0	Pt expired	Withdrew	4	5	5	5	4	0	Withdrew
Ulcer/gangrene (0 = no, 1 = yes)										
At-discharge	1	Pt expired	1	1	1	1	1	1	1	1
1 month	1	Pt expired	NA	1	1	1	0	1	1	Missed follow-up
3 months	0	Pt expired	0	1	1	1	0	1	1	Withdrew
6 months	0	NA	Withdrew	0	1	1	1	0	0	Withdrew

ATA: Anterior Tibial Artery; NA: Not Applicable; Pt: Patient

Angiographic and Clinical Endpoints

One patient died due to an unrelated cause (cardiac failure) within the first month of the study and 2 patients withdrew from the study at 1 and 6 months, respectively.

Five out of 7 patients (71%) maintained primary patency at the 6-month follow-up period. One patient presented with increased rest pain at 5 months post-enrolment. Angiogram demonstrated a severe (90%) in-stent stenosis, which was successfully treated with conventional PTA. Another patient, who was asymptomatic, had 60% in-stent stenosis noted at the scheduled 6-month follow-up angiogram, and this was treated with standard PTA.

None of the patients (7/7) underwent a major amputation until the end of the study period (6 months) as well as up to 24 months follow-up, giving a 100% limb salvage rate. Three patients underwent minor amputations (digits or forefoot) during the 24-month follow-up.

Clinical Follow-up

Of the 7 patients who completed 6 months of clinical follow-up, none showed worsening of their Rutherford score or development of new skin ischaemia during the study period. Four of the 7 patients had complete resolution of the minor tissue loss, which were present at the time of recruitment into the study. The mean baseline improvement in Rutherford score was 1.7 (range, 0-5). The clinical follow-up details are summarised in Table 3.

Complications

There were no peri-procedural access site complications. There was no incidence of acute or late in-stent thrombosis. One patient developed upper gastro-intestinal bleeding (UGIB) due to the dual antiplatelet therapy (DAPT) which settled spontaneously after withdrawal of the medications.

Discussion

Peripheral arterial disease in the Asian population involves the supra- and infra-popliteal arterial segments with diffuse heavily calcified non-occlusive pattern of disease. This is mainly due to the high prevalence of diabetes and renal failure in this group of patients which causes small vessel disease.[10,11] This is reflected in our cohort (100% were diabetic and 50% had end-stage renal failure). Singapore has a high prevalence of diabetes (11%) which is increasing.[12] A recent meta-analysis has shown that DES has significantly better long-term outcomes in diabetic patients with amputation-free survival rates of 94.1% and 90.4%, at 1 and 5 years, respectively.[13] Hence, DES may prove to be a useful treatment in our patient population to improve their clinical outcomes.

In our study, all patients presented with advanced CLI (Rutherford 5) compared to those included in the previous studies (50% to 68%).[6,7] However, our primary patency rates (71% at 6 months) are comparable to those reported in earlier trials in the Western population (86% at 6 months).[7] DES appears to be relatively safe in our small study population with no incidence of acute/late in-stent thrombosis during the follow-up period.

The limitations of our study are that it was a single arm non-randomised study design, with a small sample size and potential for selection bias. The study was limited to the evaluation of short focal lesions due to constraints of short stent lengths and the number of stents that could be used in each patient. As the evidence grows stronger in favour of DES, longer stents may become available in the future, to address the longer lesions seen in real life practice.

Conclusion

The findings of our study suggest that DES can be safely used in the treatment of BTK arterial disease in Asian CLI patients. Further large studies are required to confirm the safety and efficacy of DES in this group of patients.

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