Clinical Trials

JOURNAL OF ENDOVASCULAR THERAPY
A SAGE Publication
An official publication of the ISEVS

Journal of Endovascular Therapy
1–9

DOI: 10.1177/15266028231200466
www.jevt.org
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The Relationship Between the Global Limb Anatomic Staging System and Midterm Outcomes of Subintimal Angioplasty of Superficial Femoral Artery Atherosclerotic Disease in Chronic Limb Threatening Ischemia

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Abstract

Background: Superficial femoral artery (SFA) is commonly affected with atherosclerotic peripheral arterial disease leading to chronic limb-threatening ischemia (CLTI). Subinitimal angioplasty (SIA) is a minimally invasive option. We aimed to examine the relationship between the Global Limb Anatomic Staging System and SIA midterm limb and survival-related outcomes. **Method:** A prospective observational study was conducted on all patients with CLTI (Rutherford 4–6 or WIFI stages 2–4), with diseased femoropopliteal segment underwent SIA from August 2020 to September 2021. Patients with non-atherosclerotic SFA occlusion and those requiring primary major amputation were excluded. Multivariable Cox proportional hazard regression was performed to assess possible predictors of midterm clinical outcomes. Kaplan-Meier survival curves were used to estimate limb-based patency (LBP), limb salvage, amputation-free survival (AFS), and overall survival. **Results:** The study included 138 patients with CLTI due to chronic total occlusion of the SFA and underwent SIA ± treatment of associated ipsilateral hemodynamically significant inflow/outflow disease. Primary technical success was achieved in 116 cases (84%), with primary patency at 1, 6, and 12 months being 100%, 84%, and 79% respectively, while the limb-salvage rate at 6 and 12 months was 100% and 94%, respectively. The result of the comparison between CLASS I and Global Limb Anatomic Staging System III (GLASS III) revealed significantly worse patency with GLASS III ($p=0.005$), and better overall survival ($p=0.037$), limb salvage ($p=0.021$), and AFS ($p<0.001$) with GLASS I. **Conclusion:** Subinitimal angioplasty is a safe, effective, and minimally invasive treatment option for lengthy SFA lesions by avoiding the patients' anesthesia and operative risk. Our study suggests that the GLASS stage may be a useful predictor of midterm limb and survival-related outcomes of this approach. GLASS III anatomy in comparison with GLASS I is associated with a statistically significantly worse LBP, limb salvage, AFS, and overall survival.

Clinical Impact

This study is discussing a very hot interesting challenging topic in vascular surgery and its management as SFA atherosclerotic lesion is the most common lesion faced by vascular surgeons subintimal angioplasty SIA is considered feasible and effective method in dealing with this lesion with accepted durability and lower rates of complications.The subintimal angioplasty is made by opening an extraluminal track behind the intimal layer and between the media and intima of the artery surrounding atherosclerotic plaque and thrombus. Hence, the track has a low thrombus or plaque burden content, making the SIA easier than intraluminal angioplasty and with comparable results. GLASS stage III was an independent predictor of loss of LBP, worse AFS, and major amputation.

Keywords

SFA atherosclerotic disease, subinitimal angioplasty, GLASS, chronic limb-threatening ischemia

Introduction

The superficial femoral artery (SFA) is the most commonly affected artery by atherosclerosis, >50% of all peripheral arterial diseases (PAD).[1] It is also found that 50% of patients who undergo femoropopliteal intervention are found to have chronic total occlusions (CTO).[2] This has been attributed to many factors; first of all, SFA is one of the most extended vessels in the body that endures multiple external forces with leg movement and is surrounded by 2 major flexion points in the hip and the knee.[3,4] Moreover, it has few collateral vessels that promote more diffuse disease. Repeated injury leads to scar formation and calcification of the atheromatous plaque, and hence occlusions usually outweigh stenoses.[4]

The adductor canal has non-laminar flow dynamics, especially with walking.[5] The extent and location of lesions in the superficial femoral segment are extremely variable. Although almost half of the arterial lesions of the lower extremity were seen in the femoropopliteal area, they were rarely confined to this segment alone. However, isolated superficial femoral lesions are encountered more often in non-diabetic atherosclerotic patients than in diabetic patients.[6] A complete or nearly complete occlusion often occurs as an initial lesion at the level of the foramen adductor Magnus area.[3,4] For all these reasons, femoropopliteal lesions are one of the toughest challenges to the vascular surgeon in modern vascular surgery.

The recent Global Limb Anatomic Staging System (GLASS) resembles a comprehensive form of classification in which primary relays on a limb scheme that is focused on the best revascularization strategies in the management of critical limb-threatening ischemia (CLTI), which is different from other old classifications.[7] However, more trials are required to validate this classification and make it feasible to be used in clinical practice.

The main objective of our current study was to investigate GLASS classification and its impact on midterm limb salvage and overall survival of subintimal angioplasty (SIA) of chronic total occlusion (CTO) of SFA in patients with CLTI.

Patients and Method

We conducted a prospective study that included all patients who underwent SIA for CLTI due to atherosclerotic CTO of femoropopliteal segment presented to the Vascular and Endovascular Surgery Department, Assuit university hospital, from August 2020 to September 2021. The ethical committee of the institution approved the study.

All patients with CLTI (Fontaine III-IV, Rutherford 4–6, or with intermediate and advanced limb-threatening ischemia [WIFI stages 2–4], according to the Wound, Ischemia, and foot Infection [WIfI] classification system) who had diseased femoropopliteal segment were included, or patients with CLTI with more proximal lesions and have been addressed with successful inflow treatment. Patients with non-atherosclerotic occlusion of the SFA (thrombosis, dissection, or embolism), patients with extensive necrosis or infective gangrene requiring primary major amputation, failure of successful inflow treatment, and known intolerance to the antiplatelets or hypersensitivity to contrast agents were excluded from our study.

All patients underwent the following: detailed medical history was our first step in diagnosing CLI. The clinical picture included ischemic rest pain, ischemic ulcer, and/or gangrene. Medications in use as (anticoagulants, antithrombotic agents, statins, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin-II receptor antagonists, insulins, or oral hypoglycemic agents), and previous vascular interventions were all reported in the history. Ankle–brachial index (ABI) evaluation using Doppler was done for all patients.

As regards GLASS classification, the anatomical pattern of arterial disease was retrospectively evaluated.[7] Before the procedure, the patient's CTA was evaluated by a blinded vascular surgeon, and the result was confirmed by angiography to catch the target arterial path (TAP) to establish a continuous pulsatile flow to the foot based on the least diseased or an angiosome targeted revascularization. Then, the GLASS stage (I–III) was determined based on the scoring system for both femoropopliteal and infrapopliteal grades (0–4). Calcification was also evaluated by Peripheral Artery Calcium Scoring System (PACSS) and PARC: Peripheral Academic Research Consortium.

Electrocardiogram, chest radiograph, and basic hematologic studies such as complete blood count, fasting blood glucose, serum creatinine, fasting lipid profile, coagulation profile, and kidney function tests were done to characterize risk factors and identify end-organ involvement. Arterial duplex scanning was the primary imaging technique used to plan for the intervention in all of our patients; CTA was the second-line imaging technique used only in cases suspecting an inflow disease that could not be confirmed by duplex.

Informed consent: It was obtained from all patients before the intervention, ensuring they understood the diagnosis, the purpose of the procedure, the risks and benefits

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associated with it, the alternative treatments, and the risks and benefits of not undergoing the intervention.

Procedure technique: All patients were pretreated with acetylsalicylic acid at a mean dosage of 150 mg/day and clopidogrel at a mean dosage of 75 mg/day for at least 4 to 5 days. A nephroprotective protocol was used in all non-dialyzed patients encompassing maximizing urine outflow by infusing saline intravenously. Alternative to saline hydration, $NaHCO_3$ 154 mEq/L was given by a bolus of 3 mL/kg followed by 1 to 2 mL/kg/h for 6 hours. N-acetyl-cysteine (Mucomyst, Bristol-Myers Squibb, New York; scavenging reactive O2 species). All procedures were performed under local or regional anesthesia.

Antegrade ipsilateral percutaneous femoral access was preferred when a patent proximal segment of SFA was evident at ultrasonography. A crossover technique from contralateral CFA via long crossover sheath (45–55 cm length; Cordis Corporation, New Jersey) was used especially in cases of obese cases, total occlusion of SFA from the origin, femoral bifurcation above the inguinal ligament, and an iliac lesion that was managed before SFA treatment.

At first complete diagnostic arteriogram to allocate the occlusion site and address the distal runoff vessels. A soft, angled, hydrophilic 0.035″ guidewire (Radifocus Guidewire M Shapeable, Terumo Corporation, Tokyo, Japan) or (AQUALiner Hydrophilic Ni-Ti Alloy Guidewire; AngioDynamic Inc., Queensbury, New York) in combination with a 5-F, angled, hydrophilic catheter (Soft-Vu Berenstein Catheter; AngioDynamic incorporated, Queensbury, New York) was used to negotiate the occlusion. The subintimal plane was entered by buckling the guidewire to make a loop at its tip and trying to pass the wire supported by the catheter across the occluded vessel segment. Failed passage of the wire-catheter combination in the subintimal was solved by changing the Berenstein catheter with a support catheter (TrailBlazer Support Catheter; ev3 Endovascular, Inc. Plymouth, Minnesota). We should avoid passage of the wire far below the reentry point to avoid dissection of the runoff vessels. Difficult reentry was managed by retrograde access of the distal superficial femoral artery or tibial vessels, and Subintimal Arterial Flossing with Antegrade Retrograde Intervention technique was done.[8]

Re-entry of the catheter to the distal true lumen was achieved with the free release of the wire, passage without resistance, and evident back bleeding from the catheter. A diagnostic angiogram was performed to confirm re-entry to the distal true lumen. Balloon angioplasty of the subintimal track after the passage of the lesion and achieving distal reentry in the true lumen was ensured using 0.035″ OTW PTA dilatation catheter (EverCross 0.035″ PTA Balloon Catheter, ev3 Endovascular, Inc. Plymouth, Minnesota) (Passeo-35, Biotronik, Berlin, Germany; Wanda, Boston Scientific). The size of the balloons was 5 to 6 mm in diameter and the length was 10 to 20 cm.

Self-Expanding Nitinol stents (Protege EverFlex Self-Expanding Peripheral Stent System, ev3 Inc. Plymouth, Minnesota; E•Luminexx Vascular Stent, Bard Peripheral Vascular, Inc. Karlsruhe, Germany) were deployed selectively depending on the completion angiography and when residual stenosis more than 30%. Completion angiography at the end of the endovascular procedure was performed. Access hemostasis is achieved by manual compression. The average hospital stay in cases without complication was 2 days. Clopidogrel (75 mg/day) and aspirin 150 mg/day were continued for at least 30 days (dual anti-platelet therapy) after the interventional procedure.

Follow-up: A duplex scan was performed within 48 h of SIA and repeated at 30 days and 3, 6, 9, and 12 months. The clinical status of the patient's wound healing of minor amputations and ABI index were evaluated at the same intervals. Duplex examination was routinely used to measure the patency of the treated artery and any evidence of internal thrombus using EnVisor-C ultrasound machines (Philips Healthcare, Massachusetts) using a 3 to 12 MHz linear-array probe. The B-mode imaging frequency was 7 MHz, and the pulsed-wave Doppler frequency was 4 MHz. An insonation angle of 60 was used, with angle correction where necessary (40–60). We attempted to maintain the insonation of 60 all the time to standardize the study methodology.

End Points

To assess the immediate technical success of SIA of FP segment and to addresses the complication of the procedure and assess the relationship between GLASS stage and technical success of the procedure and the midterm result of the procedure.

Technical success can be defined as completion of the endovascular procedure and immediate morphological success with $<$30% residual diameter reduction of the treated lesion on completion of angiography, whereas failure can be defined by the inability to achieve recanalization of the femoropopliteal segment by SIA or the need for open surgical techniques to restore the antegrade flow in it.

Clinical Outcome During Follow-up

Midterm outcome measures were (a) limb-based patency (LBP), defined as continued patency of the entire TAP from groin to ankle with the absence of anatomical (occlusion, critical stenosis $>$70%, or re-intervention affecting any portion of the defined TAP), and hemodynamic failure (notable drop in ABI 0.15/TBI 0.10 or stenosis $>$50% in the TAP in the presence of recurrent or unresolved clinical symptoms

Table 1. Patients Characteristic Among the Study.

Variable	Number of patients	Percentage
Male	86	(62.3%)
Female	52	(37.7%)
Age class		
45–59 y	18	(13%)
60–75 y	62	(45%)
>75 y	58	(42%)
DM	98	(71%)
HTN	75	(54%)
CAD	59	(43%)
CRI	22	(16%)

Abbreviations: CAD, coronary artery disease; CRI, Chronic renal impairment; DM, diabetes mellitus; HTN, hypertension.

Table 2. Lesion Characteristic and Clinical Presentation Among Our Study.

Clinical	Frequency
Rest pain	34 (25%)
Ulcer	48(35%)
Gangrene	56(40%)
Length of occlusion (cm)	
<10 cm	8 (11.7%)
10–15 cm	28 (41.1%)
>15 cm	32 (47.2%)

including rest pain, worsening or persistent tissue loss);1 (b) assisted primary patency; (c) secondary patency; (d) limb salvage; (e) amputation-free survival (AFS); and (f) overall survival.

Statistical Analysis

Categorical variables are reported as numbers with percentages. Continuous variables are reported as means with standard deviation. Demographic differences were assessed with Pearson's chi-squared test for categorical variables. Multivariate analysis was performed with a Cox proportional hazards model to determine the effect of patient demographics (ie, age, sex, diabetes, and other co-morbidities), disease presentation, and treatment modality on amputation-free survival rate. All p values were considered significant at 0.05. The primary patency rate was tested on an intention-to-treat. The survival analysis techniques calculated the basis of angioplastied vessels (Kaplan-Meier curve). Statistical analyses were performed with SPSS version 20 for Mac software.

Results

The study included 138 patients suffering from CLTI due to CTO of the SFA who underwent PTA of the SFA ± treatment of associated ipsilateral hemodynamically significant inflow/outflow disease. There were 86 men (62.3%) and 52 women (37.7%) with a mean age of 71.6 years (range; 46–94 years). Gender and age distribution in the current study group is demonstrated in (Table 1). In the current study group, diabetes (the most important risk factor) was encountered in 98 (71%; Table 1). Thirty-four patients out of the 138 (25%) suffered from rest pain, 48 (35%) from lower limb ulcers, and 56 (40%) of them had digital gangrene (Table 2). Type C occlusions were encountered in 70 cases (50.7%) and type D in 78 cases (49.3%) according to the TASC morphological stratification of femoropopliteal lesions (Table 2).

Superficial femoral artery atherosclerosis was associated with inflow disease involving the ipsilateral iliac artery in 8 cases (6%), outflow disease (leg vessels) in 112 cases (81%), and both inflow and outflow disease in 4 cases (3%). Antegrade crossing of the lesion through puncturing the contralateral CFA was the most common access site used in 104 cases (75%), and combined antegrade and ipsilateral retrograde through the posterior tibial artery was used in 4 cases (3%) (Table 3). Failure of reentry to the true lumen occurred in 8 cases (6%), while successful reentry occurred in 130 cases (94%; Table 3). The 3 leg vessels were patent till the foot in 32 cases (23%), while no leg vessel was patent in 8 cases (6%; Table 3). Classification of Calcification of lesions among the studied participants (n=138) was shown in (Table 4).

Primary technical success was achieved in 116 cases (84%) (Figure 1). Out of the 22 cases where subinitmal recanalization was not possible, 14 cases underwent other successful vascular procedures in the form of 2 thrombectomy by Fogarty catheter after failed intra-arterial thrombolysis, 4 had fem-distal bypass, and 8 had fem-pop bypasses (4 of them were below the knee level using ipsilateral vein graft). The remaining 8 cases underwent major amputations (Table 5). Among the patients with immediate technical success, 18 (13%) cases had intra-operative complications and were managed successfully. Their frequency of occurrence and management are illustrated in Table 5.

During the follow-up period of our patients at the end of the 12-month period, the primary patency of the 116 cases with successful SIA at 1, 6, and 12 months was 100%, 84%, and 79% respectively (Figure 2), only 25 (21%) patients exhibited critical stenosis in already revascularized vessels. All of these cases were managed by simple ballooning.

Assisted patency rates were 100%,90%, and 85%, during the follow-up period no cases developed complete occlusion of the targeted vessel, while the limb-salvage rate at 6 and 12 months was 100% and 94%, respectively. Multivariate analysis of the relation between immediate technical success and different variables, including age, sex, risk factors, Fontaine classification, TASC classification, length of occlusion, and the number of patent leg vessels, was performed and summarized in (Tables 6-9). There were no statistically significant differences among the

Table 3. Procedural Details of Different Lesions.

Way of crossing	Frequency	Percentage
Antegrade from contralateral	104	75%
Antegrade from ipsilateral	22	16%
Combined antegrade and retrograde	12	9%
Reentry site		
Proximal pop	90	65%
Mid-pop	12	9%
Distal pop	22	16%
Tibial vessels	6	4%
No re-entry	8	6%
No. of patent leg vessels	**Frequency**	**Percentage**
Three leg vessels	32	23%
Two leg vessels	38	28%
One leg vessel	60	43%
No patent leg vessel	8	6%

Table 4. Classification of Calcification Lesions Among the Studied Participants (n=138).

Calcification Scores	N	(%)
The PARC Calcification Score		
Mild calcification	60	(43.0)
Severe calcification	78	(57.0)
PACSS grades		
0,1,2	60	(43.0)
3,4	78	(57.0)
Definitive Ca++ trial scoring		
Mild calcification	60	(43.0)
Severe calcification	78	(57.0)

Quantitative data are presented as median (range), and qualitative data are presented as number (percentage.
Abbreviations: PACSS, Peripheral Artery Calcification Scoring System; PARC, Peripheral Academic Research Consortium.

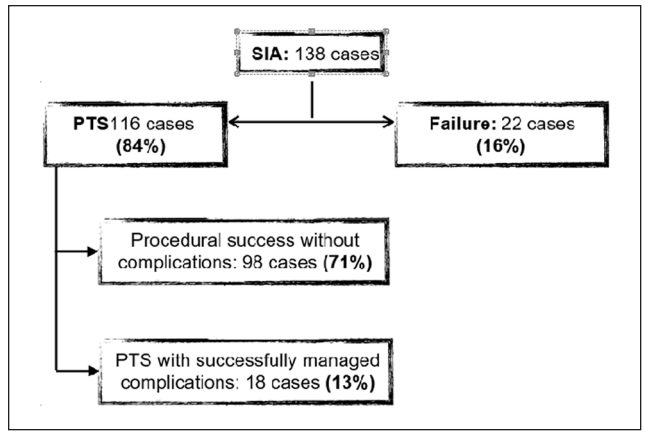

Figure 1. Flow chart showing the procedural success and failures in study group.

Table 5. Twenty-two Cases With Failed SIA, Their Management, and the Complications Rate and Their Management.

Procedure	Frequency	
Thrombectomy	2	
Fem-distal bypass	4	
Fem-pop bypass	8	
Major amputations	8	
Complication	**Frequency**	**Management**
Arterial thrombosis	4	Intra-arterial thrombolysis
AVF	4	Stent Graft
Vessel perforation	4	Prolonged ballooning try another subintimal passage
Athero-embolization	6	Push and park technique

Abbreviation: AVF, Arteriovenous fistula; SIA, subinitimal angioplasty.

GLASS stages and mid-term patency regarding baseline patient and lesion characteristics except for lesion length ($p<0.001$).

The study demographics and clinical characteristics relationship between GLASS and patency rate following SIA of CTO of SFA was shown in Tables 10 and 11. The result of comparison between CLASS 1 and GLASS III with these variables revealed significantly worse patency with GLASS III (GLASS III,33.0% vs GLASS I, 47.3%; p=0.005), better overall survival (65.7% vs 85.1%; p=0.037), limb salvage (60.8% vs 79.7%; p=0.021), and AFS (30.0% vs 66.3%; $p<0.001$) with GLASS I.

Discussion

Critical limb-threatening ischemia is the severest grade of chronic limb ischemia, which is associated with the highest threat of loss of the affected limb and is linked with the most significant morbidity and high mortality rate to patients and the health care systems. No doubt that the treatment of choice for CLTI is revascularization; however, successful revascularization for patients with CLTI has always been a challenge for the vascular surgeon, as atherosclerotic lesions associated with CLTI usually involve multiple vascular levels, requiring extensive, multilevel revascularization procedures.[9,10]

Percutaneous intervention has some advantages over surgical options especially in CLTI fragile patients like bypass by putting away the draws back of anesthesia, avoiding surgical incision in an already ischemic skin exposed to infection, and non-healing with the risk of secondary hemorrhage and with shorter hospital admission and faster recovery. SIA is now a well-known percutaneous procedure for treating long arterial occlusions. It is also called in some literature percutaneous intentional extraluminal recanalization.[11]

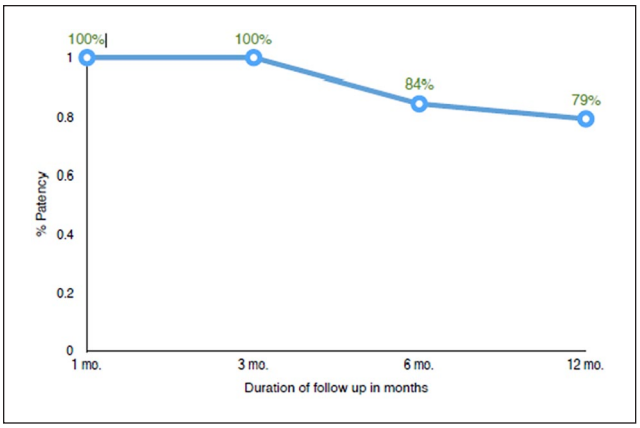

Figure 2. Kaplan-Meier curve shows cumulative patency rates for patients with Primary Technical Success.

Table 6. Age and Gender Versus Primary Technical Success.

Age class	Successful	Not successful	Total
45–59	16 (89%)	2 (11%)	18
60–75	50 (81%)	12(19%)	62
>75	50 (86%)	8 (14%)	58
Total	116 (84%)	22(16%)	138
p=0.769			
Sex	**Successful**	**Failure**	**Total**
Male	74 (86%)	12 (14%)	24
Female	42 (81%)	10 (19%)	52
Total	116 (84%)	22(16%)	138
p=0.56			

Table 7. Risk Factors Versus Primary Technical Success.

Risk factor	+/−	Frequency	PTS no. and (%)	p
DM	+ve	98	76 (77%)	0.038
	−ve	40	40 (100%)	
HTN	+ve	74	58 (78%)	0.166
	−ve	64	58 (90%)	
CAD	+ve	60	50 (83%)	0.885
	−ve	78	66 (85%)	
Renal impairment	+ve	22	18 (82%)	0.825
	−ve	116	98 (84%)	

Abbreviations: CAD, coronary artery disease; DM, diabetes mellitus; HTN, hypertension; PTS, primary technical success.

The primary outcome of our study was to confirm the efficacy and safety of SIA as a therapeutic option for the management of chronic limb-threatening ischemia (CLTI) and calculate the primary technical success, assessing the patency rate, factors affecting, and the possible complications of the procedure. Our age and sex distribution had no significant differences from the previously reported studies.

Table 8. Lesion Classification Versus Primary Technical Success.

Fontaine classification	Failed	Successful	Total
III	6 (18%)	28 (82%)	34
IV	16 (15%)	88 (85%)	104
Total	22 (16%)	116 (84%)	138
p=0.825			
TASC II classification of femoropopliteal lesions	**Not successful**	**Successful**	**Total**
Type C	8 (13%)	52 (87%)	60
Type D	14 (18%)	64 (82%)	78
Total	22 (16%)	116 (84%)	138
p=0.604			

Abbreviation: TASC II, Trans-Atlantic Inter-Society Consensus Document II.

Table 9. Length of Occlusion Versus Primary Technical Success and Number of Patent Leg Vessels Versus Primary Technical Success.

Length class	Unsuccessful	Successful	Total
Less than 10 cm	4 (25%)	12 (75%)	16
10–15 cm	4(7%)	52(93%)	56
More than 15 cm	14 (21%)	52 (79%)	66
Total	22 (16%)	116 (84%)	138
p=0.248			
Number of patents leg vessels	**Unsuccessful**	**Successful**	**Total**
0	8 (100%)	0 (0%)	8
1	6 (10%)	54 (90%)	60
2	8 (21%)	30(79%)	38
3	0 (0%)	32(100%)	32
Total	22 (16%)	116 (84%)	138
p=0.000			

The subintimal angioplasty is made by opening an extraluminal track behind the intimal layer and between the media and intima of the artery surrounding atherosclerotic plaque and thrombus. Hence, the track has a low thrombus or plaque burden content, making the SIA easier than intraluminal angioplasty and with comparable results. Previous studies reported high technical success rates with a range between 74% and 92% with a low rate of procedure complication.[12]

Taneja et al reported lengthy SFA and popliteal atherosclerotic lesions with an average lesion length of 20 cm. The 1-year patency rate was about 27%, while the limb salvage rate at 1 year was acceptable at 80%. They concluded that the SIA procedure for those lesions had a low primary patency rate with the need for repeated intervention. On the contrary, it had a high rate of limb salvage and a long duration of AFS in patients with TASC C and D disease.[13,14] Siablis et al[15] reported that factors that negatively affect

Table 10. Demographics and Clinical Characteristics of the Study Relationship Between the Global Limb: Anatomic Staging System (GLASS) and Patency Rate Following SIA of CTO of SFA.

	Overall (138)	GLASS I (19)	GLASS II (34)	GLASS III (85)	p value
Age, y					0.74
Mean ± standard deviation	65.2 ± 6.2	65.3 ± 8.1	64.6 ± 5.3	65.4 ± 6.1	
Range	53–79	53–79	55–73	55–79	
Median (interquartile range)	65 (10)	65 (14)	65 (9)	65 (10)	
Male gender	86 (62)	13 (69.0)	24 (70)	49 (58)	0.28
Diabetes	98 (71)	12 (63.1)	26 (76.4)	60 (70.5)	0.50
Hypertension	75 (54.3)	5 (27.6)	11 (32.1)	59 (69.4)	0.86
Coronary artery disease	59 (42.7)	5 (26.3)	21 (61.7)	33 (38.8)	0.85
Current smoking	103 (74.6)	12 (63.1)	27 (79.4)	64 (75.2)	0.70
CRI	22 (15.9)	3 (13.8)	6 (18.9)	13 (15.8)	0.84
Fontaine stage					0.45
Stage III	34 (24.6)	7 (37.9)	13 (37.7)	14 (16.4)	
Stage IV	104 (75.3)	12 (62.1)	23 (67.6)	69 (81.1)	

Abbreviations: CTO, chronic total occlusion; GLASS, Global Limb Anatomic Staging System; SIA, subinitimal angioplasty; SFA, superficial femoral artery.

Table 11. Characteristics of Lesions of Patients Chronic Limb Threatening Ischemia Due to CTO of SFA and Relationship Between the Global Limb Anatomic Staging System (GLASS) and Patency Rate Following SIA of CTO of SFA.

	Overall (138)	GLASS I (19)	GLASS II (34)	GLASS III (85)	p
Nature of lesion					0.40
De novo lesion	115 (83.1)	16 (86.2)	27 (79.2)	72 (84.7)	
Re-stenotic/occlusive lesion	23 (16.7)	1 (6.9)	4 (11.3)	18 (21.1)	
In stent re-stenosis/occlusion	7 (5.2)	1 (6.9)	3 (9.4)	3 (3.5)	
Lesion length (cm)					<0.001
Mean T standard deviation	27.0 ± 7.5	18.1 ± 0.9	22.3 ± 1.1	30.9 ± 6.9	
Range	17–40	17–20	20–24	22–40	
Median (interquartile range)	23 (13)	18 (2)	23 (2)	34 (14)	
Calcification, PACSS					0.088
Grade 0/1/2	60 (43.4)	3 (17.2)	4 (13.2)	53 (62.3)	
Grade 3/4	78(56.5)	10 (55.2)	19 (56.6)	49 (28.0)	
Runoff vessels					0.86
0	8 (5.7)	1(5.2)	4(11.7)	3(3.5)	
1	60 (43.3)	7 (37.9)	16 (47.2)	37 (47.5)	
2	38 (27.5)	6 (34.5)	10 (30.2)	22 (31.8)	
3	32 (23.1)	5 (27.6)	8 (22.8)	19 (31.8)	

Abbreviations: CRI, chronic renal impairment; CTO, chronic total occlusion; GLASS, Global Limb Anatomic Staging System; PACSS, Peripheral Artery Calcium Scoring System; SIA, subinitimal angioplasty; SFA, superficial femoral artery.

technical success include the presetting symptoms of CLI and the application of stent.

Hynes et al[14] reported that increasing incidence of diabetes especially with higher population ages. Diabetes is considered a well-known risk factor for increasing vessel wall calcification, affecting the vascular tree in a multilevel pattern, with infra-popliteal involvement which affects the technical success and patency rates, also higher mortality rate reaching up to 10 times higher than in non-diabetics. In the current study, we found that diabetes significantly affected the technical success of the procedure (p=0.038) with similar results reported in other studies.

In the current study, we encountered difficulty to return to the true lumen while using the antegrade access in 12/138 (9%) for which retrograde access was used as a bail-out strategy that enabled successful revascularization in 8/12 (67%), while in the other 4/12 (33%) the antegrade and retrograde catheters could not meet in the same plane (rendezvous failure), even after trying the (double-balloon) inflation technique that was described by Schmidt et al.[16]

This was similar to Ersan Tatli et al who reported that their failures were due to the inability to pass the wire in the subintimal space or return the wire intraluminal (Re-entry). He also reported a very high technical success reaching

(97%) and failed cases in the vast majority due to extreme calcification that makes the re-entry into the distal true lumen impossible.[17]

In our cohort study, multivariate analysis documented that the number of patent leg vessels significantly affected the technical success of the procedure, the same as reported in other studies as the number of patent leg vessel indicate the severity of atherosclerosis with more CLTI, and as we mentioned before, all outflow lesions were managed only in case of ulcer and gangrene in context of angiosomal concept and by simple ballooning only.

Other researchers, like London et al,[18] reported that the distal runoff, state of smoking, and lesion length predicted recurrence. Lazaris et al[19] described another trial describing SIA procedures in patients with CLI. The 1-year patency was higher in multiple runoff vessels than in single runoff vessels. It was 81% to 25% in patients' single runoff vessels.

In the current study, complications occurred in 13% (18/138) of all procedures; however, endovascular techniques managed all successfully. Complications included 4 arterial thromboses (2.9%), 4 arteriovenous fistulas (2.9%), 2 vessel perforations (2.9%), and 6 distal atheroembolization (4.3%). Arterial thrombosis occurred only in 4 cases in which a prolonged procedure was encountered to treat complex, lengthy, and multilevel lesions in obese patients, and we supposed that the heparin dose was inadequate. These cases were managed by intra-arterial thrombolysis and 2 of them were failed and treated by open thrombectomy.

The literature reports that about 15% of the approaches are complicated by a variety of complications such as access site hematoma, vessel rupture, or distal embolization. Furthermore, this is more or less like the incidence of complications after intraluminal angioplasty (11%). Although the range of complication rates is from 2% to 20% while the major complication rate is low, it must be noted that complications, such as renal failure, myocardial infarction, and even death, are underreported.[20]

SIA theoretically has a higher perforation rate than transluminal angioplasty.[21] Multiple causes can explain this; first, the subintimal angioplasty is carried out in lengthy lesions with tight occlusions, most of which have extreme calcification.[22] The forceful passage of the wire and catheter combination, which is necessary to accomplish the procedure, may increase the risk of rupture, perforation, and fistula formation[22] Also, the track between intima and media in SIA is relatively weak.[22,23] Vessel perforation occurred in 2 of our cases. This was successfully managed by taking another subintimal pass in one case and prolonged balloon inflation after successfully crossing the lesion in the other case.

Distal athero-embolization occurred in 3 cases that were successfully remedied by pushing and parking the atheroemboli in a distal unimportant (non-collateralizing vessel) tibial vessel due to the failure of retrieving it using a thrombus aspiration catheter. Surgical thrombectomy was required in one case, and it has been included in the failed group of this study as it required an open surgical technique. Failure of the procedure was encountered in 22 cases (16%) where the failure of re-entry was documented in 12 cases (9%) due to heavily calcified arteries, while thrombosis from the prolonged procedure and elastic recoil was the culprit in the other 10 cases (7%).

On multivariable Cox regression analysis, GLASS stage III was an independent predictor of loss of LBP, worse AFS, and major amputation. Patients with GLASS III had significantly worse patency when compared with GLASS I (GLASS III, 33.0% vs GLASS I, 47.3%; p=0.005), while GLASS I had a better overall survival (65.7% vs 85.1%; p=0.037), limb salvage (60.8% vs 79.7%; p=0.021), and AF) (30.0% vs 66.3%; $p<0.001$) than GLASS III. This is in accordance with the Global Vascular Guidelines, regarding the 1-year LBP, limb salvage, overall survival, and AFS.[7] Although recent studies, including our cohort, have demonstrated the GLASS stage as a useful predictor of both limb and survival-related outcomes following endovascular revascularization in patients with CLTI,[24,25] others have reported contradictory results concerning wound healing.[24] Therefore, further validation and refinement of the GLASS is crucial in larger multicenter contemporary studies.

Limitations of this study include (1) it is a single-center, single-arm study, with a moderate number of patients, and a relatively short follow-up period, (2) no drug-coated balloons (DCBs), were used in this study, (3) lack of evaluation of wound healing and interval to wound healing, and (4) no independent core lab assessment of the angiographic images was performed. However, we believe that this study provides high-level scientific data as it includes all cases with CLTI having no exclusion criteria regarding patient comorbidities or lesion characteristics, thus representing a real-world experience. Also, an advantage of this single-center study is to exclude any confounding variables that may arise when patients are treated at different hospitals.

Conclusion

According to this analysis of single center data, SIA is a safe, effective, and minimally invasive treatment option for lengthy SFA lesions by avoiding the patients' anesthesia and operative risk and can be tolerated by patients of CLTI of a fragile nature. Our study suggests that the GLASS stage may be a useful predictor of midterm limb and survival-related outcomes of this approach. GLASS III anatomy in comparison with GLASS I is associated with a statistically significantly worse LBP, limb salvage, AFS, and overall survival. Diabetes and the number of patent leg vessels have been found to significantly affect primary technical success. More studies are needed for regulation and making guidelines for follow-up and reintervention to accomplish better and longer patency rates.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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