Original Article

Major Adverse Events, Six Months after Endovascular Revascularization for Critical Limb Ischemia in Diabetic Patients

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Abstract

Background: This prospective study aimed to evaluate the detailed outcomes of diabetic patients with critical limb ischemia, six months after percutaneous transluminal angioplasty and appropriate multidisciplinary wound care.

Methods: Totally, 45 consecutive patients (50 limbs) were enrolled and then divided into two groups according to the healing of ulcers. The endpoints were ulcer healing and major adverse events including amputation, mortality, and cardiac or cerebral morbidities, during a six- month follow-up period.

Results: During six months follow-up, major amputation was performed for four of 50 limbs (8.0%). A total of nine (20%) patients died and the leading cause was cardiac death (13.3 %). Also, stroke and non-fatal myocardial infarction occurred in three (6.7 %) and one (2.2 %) of the patients, respectively. Among the 29 (59.2 %) healed wounds, 22 (44.9 %) were completely closed. The patients with nonhealing wounds had a higher rate of dialysis (40% vs. 0 %, P-value < 0.001) and more ulcers with stage of D3 according to the Texas Wound Classification (60% vs. 31 %, P-value = 0.016). Other demographic, clinical, ulcer characteristics and procedural characteristics such as number and level of the treated lesions did not differ significantly between the two groups.

Conclusion: Based on our findings, it seems that along with current usual therapeutic routines which focus on wound healing and limb salvage, more attention should be paid to simultaneous diagnostic assessments and treatment of cardiovascular disease in this group of patients during short-term follow-up.

Keywords: Diabetic foot, limb salvage, percutaneous transluminal angioplasty

Cite this article as: Kassaian SE, Mohajeri-Tehrani MR, Dehghan-Nayyeri A, Saroukhani S, Annabestani Z, Alidoosti M, et al. Major adverse events, six months after endovascular revascularization for critical limb ischemia in diabetic patients. *Arch Iran Med*. 2013; **16(5):** 258 – 263.

Introduction

Critical limb ischemia (CLI) is the most common cause for major amputation and indication for peripheral revascularization. The majority of cases of CLI are diabetic patients and CLI in this group of patients is likely to be complicated by infected nonhealing ulcers.[1, 2] Also, atherosclerosis is more diffuse and severe in diabetic patients with a tendency to involve below the knee (BTK) and small distal vessels. Nowadays, the multidisciplinary approach to diabetic foot, patient education, intensive wound care, and debridement in tandem with advances in technical options for revascularization, especially in order to access the distal arteries, can improve the limb salvage rate.[3–5] Percutaneous transluminal angioplasty (PTA) is less invasive and is repeatable in case of recurrent ulcers; moreover, it can be used in multilevel lower-limb arterial involvement and preserve the saphenous vein. Despite the technical and procedural advances in endovascular BTK revascularization, the stability and long-term patency of PTA is far from optimal, especially in diabetic patients. In addition to the higher incidence of BTK arteries lesions, in diabetic patients with CLI, collateral formation and arteriogenesis in response to ischemia is typically poor.[6,7] Therefore, the impact of peripheral revascularization on the natural history of diabetic patients with CLI remains unclear. Most of the previous studies that evaluated the outcomes dealt with freedom from amputation and survival of patients after PTA. Since diabetic patients have complex comorbidities, and their vascular system seems to be entirely involved, they are at greater risks of experiencing life-threatening ischemic cardiovascular and cerebral events. This prospective study aimed to evaluate not only the outcomes of severe ischemic diabetic foot (ulcer healing and ability to stand or walk) but also the other major adverse events including mortality and cardiac or cerebrovascular outcomes after six months in patients for whom PTA was considered as the first-line vascular procedure.

Methods

Between January and December 2010, 45 consecutive diabetic patients with CLI were referred to Tehran Heart Center for PTA from the Outpatient Diabetic Foot Clinic of the Endocrinology

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Accepted for publication: 28 December 2012

Research Center of Tehran University of Medical Sciences. All of the patients were visited in the Diabetic Foot Clinic for an initial assessment of sensory and motor neuropathy, ischemic symptoms and signs, ulcer characteristic, and control of diabetes and its complications. Simultaneously, wound care and medical treatments, including debridement of the necrotic or gangrene tissues, suitable dressing, and empirical antibiotic therapy were performed. All decisions were made under the supervision of endocrinologists, vascular surgeons, interventionists, wound care specialists, and trained nurses, according to a multidisciplinary approach which is illustrated in a previous study.[8]

Lower-limb vascular assessment

To assess the lower-limb vascular situation, color Doppler ultrasound and / or computerized tomography angiography (CTA) was performed for the patients. If there was a significant stenosis in the Doppler ultrasound or CTA which is diagnosed as the leading cause of the CLI and the ischemic ulcer by both vascular surgeon and the interventionist, the patients were subjected to digital subtraction angiography (DSA) and then PTA. Totally, 50 limbs of the 45 diabetic patients underwent multilevel angioplasties and the patients were discharged one to two days after PTA. Whether PTA was successful or unsuccessful, all the patients were referred to the Diabetic Foot Clinic for follow-up, wound care, and data collection.

Angiography and percutaneous transluminal angioplasty

All the procedures were performed under local anesthesia, and 70 IU/ kg of heparin was administered intravenously at the beginning of the procedure. PTA was utilized for all the suitable lesions with more than 70% stenosis in the angiographic assessment with no prior limitation regarding the lesion morphology. However, PTA was impossible in some conditions, because the guidewire or balloon catheter could not pass through the lesion especially in calcified occluded lesions. The antegrade approach was preferred in the majority of cases (76.43 %), but in 13.96 % of the cases retrograde and in 9.61 % of the patients both approaches were performed at the interventionist's discretion. A range of 4 – 6 F sheaths were used for vascular access. According to the lesion diameter, 0.035- or 0.014-inch guide wires were used to pass through the lesions. The balloon lengths and diameters were chosen on the basis of the vessel diameter and the lesion length. In some patients, stents were placed especially in the lesions at the iliac level. Both balloon- and self-expandable types of stents were employed but the use of balloon-expendables was dominant. The procedure was considered technically successful when a straight flow was achieved from the abdominal aorta to any infrapopliteal or collateral arteries that supplied the plantar arch or dorsalis pedis with no residual stenosis > 30%. After PTA, homeostasis was obtained via local compression. All the patients received antiplatelet therapy (aspirin 80mg and clopidogrel 75mg per day) at least for one month after PTA, and the long-term use of aspirin was recommended.

Follow-up

All the patients were visited in the Outpatient Diabetic Foot Clinic early after discharge and subsequently at one and six months after PTA. More visits were planned if necessary according to the ulcer and patient's situation. Standard wound care (dressing, infection control, and debridement), glycemic control, and management of hyperlipidemia and hypertension, if needed, were performed during the follow-up visits. Short- and mid-term clinical success was defined based on the ulcer appearance, ulcer size, reduction of rest pain, and, of course, limb salvage. Routine angiography or Doppler ultrasound was not performed at follow-up, unless any symptom or sign of restenosis (such as recurrent rest pain or ulcer and worsening ulcers) was observed during the follow-up.

Outcomes and definitions

The primary endpoints of the present study were ulcer healing, major amputation, and mortality during a six-month follow-up period. The main goal was to preserve the lower-limb function, including standing and walking without pain, and promotion of ulcer healing. Ulcer healing was defined as at least 30 % reduction of ulcer size without any necrosis or inflammatory symptoms while infection was controlled with suitable antibiotic treatment and no major amputation and revascularization, including re-PTA or bypass grafting. Any unhealed ulcer during follow- up, without a need for major amputation, was considered as nonhealing. Any amputation at or above the ankle was considered as a major amputation. Minor amputation was defined as any toe or transmetatarsal amputation when the plantar stance was preserved. Date and the cause of death were recorded in case of mortality. Events like myocardial infarction (MI) or cerebrovascular accident (CVA) were registered by the physician, who diagnosed them through the clinical visits or telephone contacts during the follow-up period.

Statistical analysis

The results are presented as mean ± standard deviation (SD) for the quantitative variables and are summarized by raw numbers and percentages for the categorical variables. The continuous variables were compared using the Student *t*-test or Mann- Whitney *U* test when the presumption of normality was violated, while the categorical variables were compared using the *chi*-square test or *Fisher* exact test when the criteria for using *chi*-square were not met, across the two groups of healing and nonhealing patients.

Freedom from major amputation and patient survival during the six-month follow-up period were estimated using the Kaplan-Meier method, the standard estimator of the survival function.

For the statistical analysis, the statistical software SPSS version 15 for Windows (SPSS Inc., Chicago, IL) was used. All the P-values were two-tailed, with statistical significance defined by a P- value ≤ 0.05.

Results

The demographic and clinical characteristics of the patients are represented in Table 1. Totally, 50 limbs of the 45 patients with a mean age of 64.34 ± 14.75 years were treated. Most of the patients were men (76 %). The duration of diabetes was 20.68 ± 9.79 years, and 55.8 % of the patients were insulin dependent. Almost 70 % of the patients had a positive history of hypertension and were under antihypertensive treatment. History of hyperlipidemia, coronary artery disease, and stroke was positive in 56.3, 42.6, and 13.6 % of the patients, respectively, and 4% of the study population were current smokers.

With respect to ulcer characteristics, 28.6% of the patients presented with ulcers larger than 5 cm^2. Rate of infection and osteomyelitis was 57.1 and 12%, respectively. Most of the ulcers were

neuroischemic (77.8 %), in the class of D3 according to the Texas Wound Classification (42 %) and located in toes (72.9 %). Ulcer duration was more than three months in 45.7 % of the patients. The follow-up rate was 97.78 %, and one of the 45 patients was lost to follow-up (mean follow- up 6.34 ± 1.03 months). Totally, ulcers of 29 patients were healed during follow- up period. The patients were divided into two groups according to the healing of ulcers. A comparison between the two groups demonstrated that the patients with non-healing wounds had a higher rate of dialysis (40% vs. 0 %, P- value > 0.001) and more ulcers with stage of D3 according to the Texas Wound Classification (60% vs. 31 %, P- value = 0.016). The other demographic, clinical, and ulcer characteristics did not differ significantly between the two groups (Table 1).

Any vessel with stenosis more than 70 % of the diameter was regarded as an involved vessel. The selection of which lesion of which vessel should be subjected to peripheral angioplasty was based on the interventionist's decision considering the location of the ulcers, situation of the vessels distal to the obstruction, and feasibility of the procedure. The comparisons of the PTA characteristics between the healed and nonhealed wounds are shown in Table 2. There was no significant difference between the two groups of patients regarding the procedural characteristics (Table 2).

Table 1. Baseline demographic, clinical, and ulcer characteristics

Variables	Total † (n = 50)	Healing (n = 29)	Nonhealing (n = 20)	P-value
Demographic				
Age	64.34 ± 14.75	65.24 ± 11.07	62.65 ± 19.32	**0.554**
Age over 80 years	8 (16.0)	4 (13.8)	4 (20.0)	**0.700**
Male gender	38 (76.0)	21 (72.4)	16 (80.0)	**0.738**
BMI	25.19 ± 4.37	25.76 ± 4.11	24.39 ± 4.72	**0.328**
BMI > 30	5 (12.2)	3 (12.5)	2 (11.8)	**0.999**
Patient's status				
Bedridden	0 (0.0)	0 (0.0)	0 (0.0)	**0.999**
Wheelchair	10 (20.0)	5 (17.2)	4 (20.0)	
Ambulatory	40 (80.0)	24 (82.8)	16 (80)	
Clinical				
DM duration (years)	20.68 ± 9.79	20.41 ± 9.05	20.58 ± 11.02	**0.954**
Insulin therapy	24 (55.8)	14 (50.0)	10 (71.4)	**0.186**
Neuropathy	41 (89.1)	25 (92.6)	16 (84.2)	**0.635**
Nephropathy				**0.362**
Creatinine > 1.5	16 (32.0)	8 (27.6)	8 (40.0)	
Creatinine ≤ 1.5	34 (68.0)	21 (72.4)	12 (60.0)	
Dialysis	8 (23.5)	0 (0.0)	8 (53.3)	**< 0.001**
Current smoker	2 (4.1)	0 (0.0)	2 (10.0)	**NS**
Addiction	3 (6.3)	2 (7.1)	1 (5.3)	**0.999**
Hx of HTN	33 (67.3)	21 (75.0)	12 (60.0)	**0.269**
Hx of hyperlipidemia	27 (56.3)	20 (71.4)	6 (31.6)	**0.007**
Hx of coronary artery disease	20 (42.6)	13 (46.4)	6 (33.3)	**0.379**
Previous CAG	9 (18.4)	8 (27.6)	1 (5.0)	
Previous PCI	1 (2.0)	0 (0)	1 (5.0)	
Previous CABG	7 (14.3)	5 (17.2)	2 (10.0)	
Hx of stroke	6 (13.6)	3 (12.5)	2 (10.5)	**0.999**
Hx of anemia	5 (10.0)	3 (10.3)	3 (10.0)	**0.999**
Hb < 11.8 before PTA (median)	25 (50.0)	14 (48.3)	10 (50.0)	**0.906**
Ulcer				
Ulcer etiology				
Ischemic	10 (22.2)	7 (25.9)	3 (16.7)	**0.464**
Neuroischemic	35 (77.8)	20 (74.1)	15 (83.3)	
Ulcer duration > 3 months	21 (45.7)	11 (40.7)	9 (50.0)	**0.540**
Ischemic rest pain	16 (43.2)	8 (36.4)	8 (53.3)	**0.306**
Ulcer size > 5cm²	14 (28.6)	9 (31.0)	5 (26.3)	**0.726**
Infection	28 (57.1)	17 (58.6)	11 (57.9)	**0.960**
Osteomyelitis	6 (12.0)	3 (10.3)	3 (15.0)	**0.677**
Ulcer site				
Toes	35 (72.9)	20 (69.0)	15 (77.8)	**0.379**
Other	13 (27.1)	9 (31.0)	4 (22.2)	
Texas Wound Classification				
D3	21 (60.0)	9 (31.0)	12 (60.0)	**0.016**
Baseline ABI				
< 0.5	8 (20.5)	4 (17.4)	4 (25.0)	**0.293**
0.5 – 0.9	18 (46.2)	13 (56.5)	5 (31.3)	
> 0.9	13 (33.3)	6 (26.1)	7 (43.8)	
Hx of major amputation in the contralateral limb	5 (10.0)	2 (6.9)	3 (15.0)	**0.387**

BMI= Body Mass Index; DM= Diabetes Mellitus; HTN= Hypertension; CAG= Coronary Angiography; PCI= Percutaneous Coronary Intervention; CABG= Coronary Artery Bypass Grafting; Hb= Hemoglobin; PTA= Percutaneous Transluminal Angioplasty; ABI= Ankle Brachial Index; NS= Not Significant. Data are given as mean ± standard deviation or n (%). † The difference between the total number of patients and the sum of patients in the healing and nonhealing groups is because of the loss of one patient to follow- up. Thus, no data were available about the ulcer healing of that patient.

Table 2. Procedural characteristics

Variables	Total † (n = 50)	Healing (n = 29)	Nonhealing (n = 20)	P-value
No. of vessel treated				
1	18 (38.3)	11(40.7)	7 (36.8)	**0.916**
≥ 2	29 (61.7)	16 (59.3)	12 (63.2)	
Level of PTA				**0.416**
ATK	11 (22.0)	8 (27.6)	3 (15.0)	
BTK	25 (50.0)	15 (51.7)	10 (50)	
BTK + ATK	14 (28.0)	6 (20.7)	7 (35)	
Stent use (%)	12 (24.0)	8 (27.6)	4 (26)	**0.738**
PTA technical failure	3 (6.0)	2 (6.9)	1 (5)	**0.999**

PTA= Percutaneous Transluminal Angioplasty; ATK= Above The Knee; BTK= Below The Knee. Data are given as n (%). †The difference between the total number of patients and the sum of patients in the healing and nonhealing groups is because of the loss of one patient to follow- up. Thus, no data were available about the ulcer healing of that patient.

All patients with infected ulcers received oral antibiotic therapy until the infection had been cleared. Surgical debridement and even minor amputations were performed if necessary. Table 3 shows that, among 29 (59.2 %) healed wounds, 22 (44.9 %) were completely closed. Major amputation was performed for four (8.0%) patients, one of them died while amputation was performing. A minor amputation was performed, in terms of limb salvage, for six patients (12.0%). A total of nine (20%) patients died. The leading cause of death was MI and cardiac death (13.3 %). Other patients' mortality was related to diabetic foot complications such as sepsis or major amputation. It is notable that, there were other cardiovascular events, such as stroke or nonfatal MI in three (6.7%) and one (2.2 %) of the patients, respectively which occurred during the follow- up period. The Kaplan-Meier cumulative survival and amputation- free survival estimates are shown in Figure 1. The cumulative survival at six months was 91.6 % (standard error (SE): 4 %) and the amputation- free survival at the same period was 78.8 % (SE: 6.3%).

Discussion

Initiation of CLI in diabetic patients is a dramatic event because it is associated with decreased quality of life and increased risk of amputation and mortality.[9,10] In the majority of cases, infection and enlargement of a small skin ulcer, followed by gangrene, is responsible for the lower-limb amputation.[11] Although, according to the recent literature, there is confusion about indications and results of endovascular treatment, the evidence that distal arterial revascularization offers the best choice for limb salvage in diabetic patients with CLI is increasing.[1,12–14] Even today, there is a dearth of studies investigating detailed outcomes such as healing, major amputation, and mortality, and how they are influenced by different factors. According to our results, there was no significant difference between the healing and nonhealing groups of the patients regarding most of the baseline ulcer characteristics, including the etiology, duration, size, and site of the ulcer. The other baseline clinical characteristics were not different between the two groups, except for the presence of dialysis and the infections deep in the bone (D3 according to the Texas Wound Classification), which were the factors that negatively influenced the healing of ulcer. This implies that Texas Wound Classification is accompanied with prognosis regarding the risk for major amputation (Table 1). Percutaneous angioplasty was performed in all the patients with no limitation for long, calcified, or multiple and

Table 3. Outcomes at six months of follow- up

Outcomes	n (%)
(n = 49 limbs)†	
Healing	29 (59.2)
Complete healing	22 (44.9)
Ulcer reduce	7 (14.3)
Nonhealing	20 (40.8)
Amputation	10 (20.4)
Minor	6 (12.2)
Major	4 (8.2)
(n = 44 patients)†	
Mortality	9 (20.0)
Related to disease	3 (6.7)
Amputation	2 (4.4)
Sepsis	1 (2.2)
Nonrelated to disease	6 (13.3)
MI	6 (13.3)
Other cause	---
Mortality and amputation	2 (4.4)
CVA during follow- up	3 (6.7)
Nonfatal MI during follow- up	1 (2.2)

MI= Myocardial Infarction; CVA= Cerebrovascular Accident. † Since one of the patients was lost to follow- up, no data were available about the outcome. Therefore, that patient was not included in this analysis.

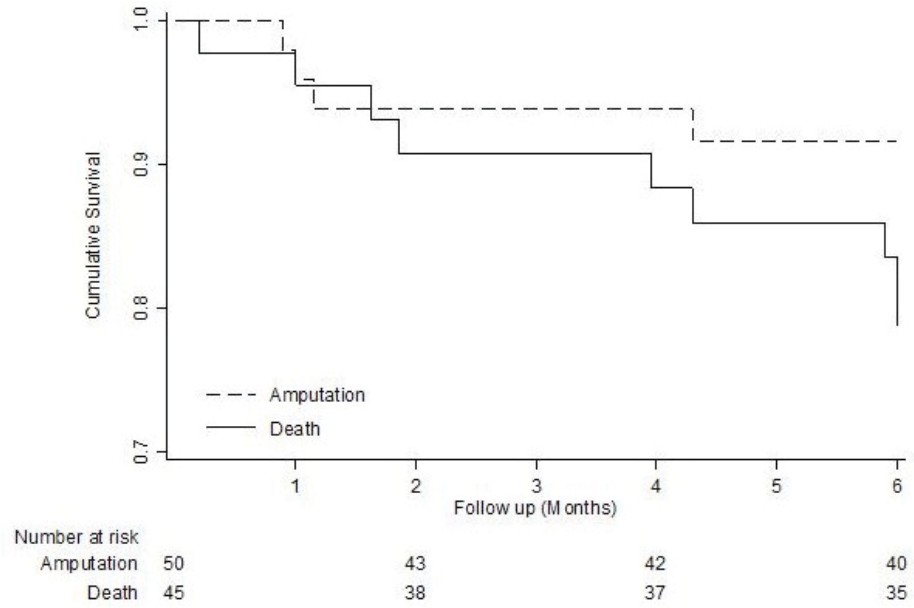

Figure 1. The Kaplan-Meier cumulative survival and amputation- free survival estimates in diabetic CLI patients who underwent PTA.

multilevel lesions. The procedural characteristics did not differ significantly between the two groups of patients (Table 2). The rate of limb salvage after the six-month follow-up was 92%. Totally, 59.2% of the ulcers were healed, of which 44.9 % were completely closed. Mortality was in consequence of CLI and amputation, only in 6.7% of total mortalities (20.0%). MI was the leading cause of mortality. Moreover, nonfatal MI and stroke occurred in 2.2 and 6.7% of the patients, respectively, during the six-month follow–up (Table 3).

Our main results, including limb salvage, major amputation, ulcer healing, and mortality, were in accordance with those reported in the literature. In a review of ten largest studies on the endovascular treatment of CLI by Graziani, et al. the limb salvage rate was in the range of 80% – 98% at six to 18 months of follow-up.[6, 15–18] Another study reported a limb salvage rate of 82% at six months after PTA.[19] Our study is one of the few studies to have evaluated the cardiovascular outcome in diabetic patients undergoing endovascular treatment for CLI. In our study, the remarkable incidence of cardiac and cerebral events during the follow-up period implies that more attention should be paid to investigate these events. Diabetic CLI patients often suffer from extensive comorbidities. Recent studies have demonstrated that the limb ischemia is actually a marker of cardiovascular disease with a high incidence of acute cardiovascular events and also generalized atherosclerosis.[20–22] In a study by Flu, et al. no difference was seen in the occurrence of adverse events, including cardiac events in all CLI patients undergoing primary revascularization by PTA vs. bypass graft procedure.[10] This finding suggests that although PTA is known as a less invasive technique which is not done under general anesthesia and is accompanied by fewer in-hospital or early complications and events, postdischarge events, especially those relating to atherosclerosis such as MI or stroke, should not be underestimated. In addition to diabetes and other cardiovascular risk factors like hyperlipidemia and hypertension in diabetic CLI patients, another possible explanation for the high incidence of postdischarge cardiovascular events is the inflammatory response after PTA. Although the long-term effect of this inflammatory state is unclear, it may cause instability of the chronic atherosclerotic plaques in the coronary or carotid arteries that were stable before angioplasty and render patients prone to cardiovascular events in the future.[23–25] Future studies should investigate whether the simultaneous limb and cardiovascular events are the results of the probable early stimulation of the systemic inflammation response by PTA or are the markers of chronic inflammatory state, which influences the development of vulnerable atherosclerotic plaques. In line with the aforementioned studies and considering the probability of silent ischemia in diabetic patients with no history of coronary artery disease, invasive or noninvasive cardiovascular evaluation and management of the related risk factors, would be beneficial to control the potential risk of postprocedural adverse events. Moreover, initiation or improvement of suitable treatments of cardiovascular disease could increase the survival rate in high-risk patients and should be deemed as an important goal along with therapeutic approaches focusing on wound healing and limb salvage in diabetic CLI patients. Future investigations are needed to clarify the impact of simultaneous assessment and treatment of cardiovascular disease in the prevention of adverse outcomes in diabetic CLI patients undergoing PTA.

Our prospective study has some limitations. The Ankle Brachial Index (ABI) and toe pressure are not accurate enough to evaluate peripheral arterial disease (PAD) in diabetic patients with CLI. The first reason is the chronic calcified atherosclerotic arteries which cause the ABI to be measured false positive. The other problem is that patients who refer to a diabetic foot clinic often present with chronic wounds, inflammation, and previous amputations, so that determining the ABI and toe pressure is impossible in one-third of cases because of the absence of at least one proper pressure measurement. However, previous studies have also revealed that when the ABI can be determined, it underestimates the severity of PAD as seen on angiography.[21] Transcutaneous oxygen (TCPO2), as a more accurate measure, was not available in our center at the time of study. Furthermore, the follow-up time of six

months may be relatively short and further follow-up is necessary to evaluate the long-term outcome. Nonetheless, a high follow-up rate was an advantage for this study. Finally, it is deserving of note that the number of cases was relatively small in this study and future studies with a larger sample size and long-term follow-up periods are necessary.

Conclusion

Lower- limb arteries PTA in diabetic patients with CLI provides a good primary success rate and rare need for major amputation. However, high incidence of the cardiovascular events which results in mortality and morbidity few months after PTA, notifies that along with current usual therapeutic routines which focus on wound healing and limb salvage, more attention should be paid to simultaneous diagnostic assessment and treatment of cardiovascular disease in this group of patients during the short- term follow- up. Prospective studies are needed to investigate the efficacy of the simultaneous diagnostic assessment and treatment of cardiovascular disease in this group of patients.

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