Long-Term Cilostazol Treatment and Predictive Factors on Outcomes of Endovascular Intervention in Patients with Diabetes Mellitus and Critical Limb Ischemia

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ABSTRACT

Introduction: Despite improvements in endovascular interventions and multidisciplinary approaches, improving clinical outcomes and increasing limb salvage have become increasingly challenging. This prospective study investigated the associations of cilostazol treatment with clinical outcomes and predictive factors in patients with diabetes mellitus (DM) and critical limb ischemia (CLI) after endovascular revascularization of the affected angiosome.

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Methods: In this study, 172 consecutive patients with CLI (Fontaine levels III–IV) received cilostazol treatment after successful endovascular intervention according to the angiosome concept, and their primary patency rates and cardiovascular and amputation events during a 24-month follow-up period were assessed.
Result: The 24-month primary patency rate, mortality rate, and amputation rate were better in the patients under long-term cilostazol treatment ($P < 0.001$, $P = 0.029$, and $P = 0.014$). Weighted multivariate Cox analyses with a propensity scoring-based method showed that long-term cilostazol treatment [hazard ratio (HR) 0.2, 95% confidence interval (CI) 0.11–0.36, $P < 0.001$], direct revascularization (DR) (HR 0.46, 95% CI 0.28–0.74, $P = 0.002$), and supervised exercise (HR 0.4, 95% CI 0.24–0.66, $P < 0.001$) were independently associated with primary patency. Patients with lower-extremity amputation (LEA)

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had a higher risk of coronary artery disease (CAD) and mortality. Cellulitis and neuropathy were independently associated with LEA events (cellulitis: HR 2.89, 95% CI 1.66–5.05, $P < 0.001$; neuropathy: HR 2.2, 95% CI 1.31–3.7, $P = 0.003$). *Conclusion*: Our results showed that patients with DM who received cilostazol treatment for more than 3 months had significantly better outcomes and decreased amputation and mortality rates after DR, and cellulitis and neuropathy were highly associated with the risk of limb loss. A large-scale randomized trial should be conducted in the future to confirm these results. *Trial Registration*: Taipei Veterans General Hospital (TVGH) IRB no. 2013-08-020B. Registered 30 August 2013.

Keywords: Coronary artery disease; Critical limb ischemia; Diabetes mellitus; Indirect and direct revascularization; Lower-extremity amputation

Key Summary Points

Why carry out this study?

Despite improvements in endovascular interventions and multidisciplinary approaches, maintaining clinical outcomes and prevention of limb loss have become increasingly challenging in patients with DM and critical limb ischemia (CLI).

This prospective study investigated the associations of cilostazol treatment with clinical outcomes and predictive factors in patients with diabetes mellitus (DM) and critical limb ischemia (CLI) after endovascular revascularization of the affected angiosome.

What was learned from the study?

Weighted multivariate Cox analyses with a propensity scoring-based method showed that long-term cilostazol treatment, direct revascularization (DR), and supervised exercise were independently associated with primary patency. The 24-month primary patency rate, mortality rate, and amputation rate were better in patients under long-term cilostazol treatment.

Our study concluded that cilostazol treatment for more than 3 months and direct revascularization of the affected angiosome should be considered for patients with DM and CLI to maximize clinical outcomes and prevent further tissue loss. A large-scale randomized trial should be conducted in the future to confirm these results.

INTRODUCTION

Currently, approximately 2.3 million individuals in Taiwan have been diagnosed with diabetes mellitus (DM), the equivalent of 1 in 10 adults. The annual diagnosis rate of approximately 25,000 cases continues to increase according to figures reported by the Health Promotion Administration, Ministry of Health and Welfare. Type 2 DM is associated with increased risks of macrovascular complications (such as stroke, cardiovascular disease, and heart failure) and microvascular complications (including retinopathy, neuropathy, lower-limb amputation, and kidney failure). Diabetic foot (DM foot) combined with ischemia, namely critical limb ischemia (CLI), is a severe form of peripheral arterial occlusive disease (PAOD) caused by atherosclerosis, which is similar to other cardiovascular diseases, and thereby may act as a predictor of premature cardiovascular events [1–5]. Patients with DM who have PAOD usually present with atypical leg pain or intermittent claudication, and do not receive a timely diagnosis and treatment until the disease progresses [2, 6, 7]. DM foot with CLI manifests as ischemic ulceration, gangrene, and rest pain, and is associated with high rates of cardiovascular mortality and lower-extremity amputation (LEA) [8, 9]; urgent revascularization is frequently required for limb salvage and preservation of quality of life. Despite recent advances in surgical and endovascular techniques, the clinical outcome of CLI in patients with DM is still inconsistent.

Numerous studies have reported that individuals with DM foot and CLI have multiple predisposing factors and comorbidities, such as cellulitis, neuropathy, coronary artery disease (CAD), stroke, and chronic kidney disease (CKD), which can complicate treatment and potentially worsen the clinical outcome [10–15].

Even in patients who undergo successful revascularization for limb salvage, most still have claudication after the operation. Cilostazol treatment has been routinely applied in patients with PAOD and DM to improve intermittent claudication and increase their walking distance. Additionally, recent papers have suggested that cilostazol treatment may improve stent patency in coronary arteries or peripheral arteries [16–20]. To the best of our knowledge, information regarding the clinical outcomes of cilostazol treatment in the management of CLI is limited. Therefore, we hypothesized that long-term cilostazol treatment may improve the clinical outcome of patients with DM and CLI who receive endovascular intervention of the affected angiosome, along with risk factor modification, supervised exercise, prompt management of infections, and aggressive wound care.

Therefore, the purpose of this study was to investigate the associations of cilostazol treatment and predictive factors with maximization of beneficial clinical outcomes and maintenance of limb function in patients with DM and CLI after endovascular revascularization of the affected angiosome.

METHODS

Study Population

The Institutional Review Board (IRB) of Taipei Veterans General Hospital, Taiwan, approved this prospective, non-randomized study (IRB no. 2013-08-020B), in agreement with the Declaration of Helsinki. All participants provided written informed consent to participate in this study. From September 2013 to December 2017, 205 patients with DM and CLI were treated in a single medical center; of these, 33 patients did

not satisfy the inclusion criteria, resulting in 172 patients being included in this study (Fig. 1). The inclusion criteria were patients aged 20–90 years; those with a first diagnosis of PAOD; those with DM; those with CLI (Fontaine class III and IV); those with tissue loss associated with an ankle pressure less than 70 mmHg or a toe pressure less than 50 mmHg; those who underwent infrapopliteal artery intervention alone or combined with femoropopliteal or iliofemoral artery intervention; those who underwent successful endovascular revascularization (defined as less than 30% residual stenosis on angiography, with evidence of a minimum of one tibial artery to the foot) [21]; those able and willing to perform regular exercise; and those who received cilostazol treatment after the intervention. Patients with acute artery embolism; those with Buerger's disease; those who had undergone prior amputation (minor or major); those with congestive heart failure (CHF) according to New York Heart Association (NYHA) function III–IV or an ejection fraction of less than 35%; those with bleeding diathesis, acute cardiovascular diseases, or acute cerebrovascular diseases; and those with active diseases such as hepatitis, malignancy, or systemic infection were excluded.
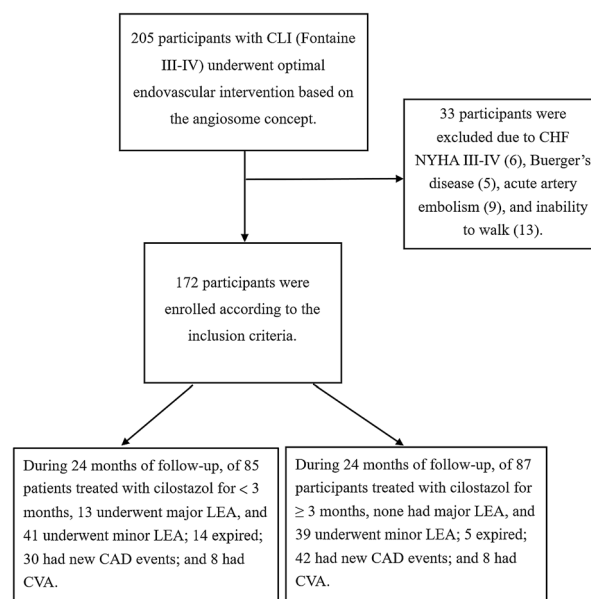
Fig. 1 Flow diagram of the study

The National Health Insurance (NHI) administration suggests that cilostazol is indicated in patients with intermittent claudication, leg pain, or numbness related to PAOD in Taiwan.

Accordingly, after successful intervention, all patients were treated with cilostazol, the duration of treatment being based on resolution of the symptoms of claudication, leg pain, and numbness. If patients had resolution or reduction of symptoms along with a normal ankle brachial index (ABI) or sonographic findings, cilostazol treatment would be administered for 2–3 months. If symptoms persisted or abnormal findings were detected, cilostazol treatment would be administered for more than 3 months.

Thus, the patients in this study were divided into control and cilostazol groups according to the duration of cilostazol treatment. Patients in the cilostazol (long-term) group were treated with cilostazol for more than 3 months, while participants in the control (short-term) group were treated with cilostazol for 2–3 months (at most 3 months).

Study Design

The diagnosis and validation of CLI (defined as a Fontaine stage III or higher) were confirmed at our outpatient clinic according to clinical evaluation, duplex scanning, or the ABI and computed tomography angiography (CTA) [21, 22]. Peripheral neuropathy was diagnosed using tests such as a nerve conduction test and electromyography. Diabetic retinopathy is confined to the retina, which is damaged as a result of DM. This medical condition was diagnosed by an ophthalmologist by initially performing a dilated exam, and then a comprehensive eye examination.

The anatomical inclusion criteria, according to CTA performed prior to intervention, were based on an infrapopliteal artery intervention alone or combined with femoropopliteal or iliofemoral artery intervention.

The severity of ischemia and the involved lesion were stratified on the basis of the Wound, Ischemia, Foot Infection classification system of the Society for Vascular Surgery and the Trans-

Atlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) classification [21–23]. In this study, patients with severe arterial calcification were classified on the basis of the Peripheral Academic Research Consortium Lesion and Vessel Characteristics and Definitions [24–26].

Revascularization can be divided into direct revascularization (DR) and indirect revascularization (IR) according to the angiosome concept. DR provides adequate blood flow directly to the area of ischemic tissue in patients with CLI, whereas IR supplies blood flow through collaterals to the ischemic limb [27–29].

Medication and Physical Management

Dual antiplatelet therapy was administered to patients undergoing stent implantation for at least 3 months, and single antiplatelet therapy was given later. Single antiplatelet therapy was prescribed to patients undergoing a simple angioplasty. All patients in this study received cilostazol treatment (50–100 mg bid) after the intervention.

According to the practice guidelines and published reports of the American College of Cardiology/American Heart Association (ACC/AHA) [30–32], all patients were advised to perform exercise or walk. After revascularization, a rehabilitation physician was consulted, who collaborated to check each patient's condition and arrange a series of exercise therapy interventions. All of the enrolled patients and their families were routinely questioned to determine whether the patients were compliant regarding exercise every month at the outpatient office or by telephone.

Study Endpoints

The primary endpoints were the primary patency rates at 6, 12, 18, and 24 months; secondary patency rates at 12 and 24 months; and amputation rate at 24 months. LEA in this study was defined as minor (below the ankle) or major (above the ankle) amputation. The secondary endpoints were overall survival (OS) or overall mortality associated with cardiovascular events

or sepsis as a result of DM foot, overall amputation-free survival, cerebrovascular accident (CVA) at 24 months, and CAD at 12 and 24 months. Notably, amputation-free survival (AFS) in this study was defined as the avoidance of minor and major amputation.

All patients underwent clinical, ABI, and Doppler ultrasound examinations upon discharge and after 3, 6, 12, and 24 months. If abnormal findings were obtained, CTA or invasive angiography was performed. Patency failure was defined as (1) a decrease in the ABI by 0.10 during follow-up or a return to the preprocedure level; (2) duplex ultrasonography findings of at most a 50% stenosis diameter of the treated segments according to a peak systolic velocity index (intrastenotic peak systolic/prestenotic ratio) of less than 2.4; or (3) CTA or invasive angiography findings indicating a stenosis diameter of at most 50% or an area of stenosis of at most 70% [25, 33].

Statistical Analysis

Continuous data are presented as mean $\pm$ SD, and categorical data are presented as percentages. The Kolmogorov–Smirnov test was used to analyze the normality of numerical variable distributions. With regard to numerical variables, the Mann–Whitney U test and independent samples t test were used to determine intergroup differences. Frequencies and categorical variables were compared using the chi-square test. Kaplan–Meier curves were obtained for time-to-patency analysis. Patients being followed-up were censored at the time of death, major amputation, or patency failure for cumulative patency.

Predisposing factors of primary patency and amputation at 24 months were confirmed through univariate Cox regression. Furthermore, these significant factors and potential factors with P values of less than 0.15 were analyzed using a weighted multivariate Cox regression model to evaluate the associations with primary patency and amputation according to the average treatment effect (ATE) or the average treatment effect on the treated (ATT). Inverse probability weighting propensity scores (PS) were calculated on the basis of disease severity and location using logistic regression to estimate the ATE or the ATT.

A P value of less than 0.05 was deemed significant. All analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

In total, 205 patients with DM and CLI were treated with endovascular revascularization at a single medical center, and 33 patients were excluded on the basis of the study criteria. All 172 patients who were eligible for inclusion were analyzed, and underwent a comprehensive follow-up for 24 months. The mean follow-up period was 3.46 ± 1.2 years. A flow diagram of this study is shown in Fig. 1.

Data on the baseline demographic and clinical characteristics of the patients associated with cilostazol treatment for at most 3 months and more than 3 months are summarized in Table 1. After successful interventions based on the angiosome concept, the patients were divided into two groups according to the duration of cilostazol treatment. The cilostazol group included 87 participants treated with cilostazol for more than 3 months (long-term: cilostazol group), while the control group included 85 subjects treated with cilostazol for at most 3 months (short-term: control group).

The study sample comprised 59 women and 113 men, with a mean age of 73.1 ± 9.6 years (range 49–90 years). The mean ages of the patients in the cilostazol and control groups were 73.9 ± 9.7 and 72.2 ± 9.5 years ($P = 0.234$), respectively. Overall, 146 (84.9%), 87 (50.9%), and 64 (37.2%) patients had hypertension, hyperlipidemia, and a positive smoking status, respectively. In addition, 62 patients (36%) had CAD at baseline, 73 (42.4%) had end-stage renal disease (ESRD) requiring regular dialysis, 62 (36%) had diabetic retinopathy, 81 (47.1%) had neuropathy, and 100 (58.1%) had cellulitis.

In a subgroup analysis of the duration of cilostazol treatment, 36 (41.4%), 46 (52.9%), 36 (41.4%), 43 (49.4%), 36 (65.5%), 59 (67.8%), 38 (43.7%), and 35 (40.2%) patients in the

Table 1 Baseline demographic data and characteristics associated with cilostazol treatment for at most 3 months and more than 3 months

Characteristic	Total population (n = 172)	Control group (n = 85)	Cilostazol group (n = 87)	P value
Age, years	73.1 ± 9.6	72.2 ± 9.5	73.9 ± 9.7	0.234
BMI	24.8 ± 3.8	25 ± 3.4	24.5 ± 4.2	0.431
SBP	136.1 ± 20.9	136.9 ± 17.7	135.3 ± 23.7	0.632
Gender (female)	60 (34.9)	34 (40)	26 (29.9)	0.164
Lesion site (left)	98 (57.0)	49 (57.6)	49 (56.3)	0.861
Baseline CAD	62 (36.0)	33 (38.8)	29 (33.3)	0.453
ESRD (regular dialysis)	73 (42.4)	37 (43.5)	36 (41.4)	0.775
Hypertension	146 (84.9)	74 (87.1)	72 (82.8)	0.431
Hyperlipidemia	87 (50.9)	43 (51.2)	44 (50.6)	0.936
Baseline CVA	25 (14.5)	14 (16.5)	11 (12.6)	0.476
Smoking	64 (37.2)	33 (38.8)	31 (35.6)	0.665
Cellulitis on presentation	100 (58.1)	54 (63.5)	46 (52.9)	0.157
Atrial fibrillation	23 (13.4)	8 (9.4)	15 (17.2)	0.131
Baseline ABI	0.52 ± 0.15	0.51 ± 0.15	0.53 ± 0.15	0.473
Calcification	75 (43.6)	36 (42.4)	39 (44.8)	0.744
Retinopathy	62 (36)	26 (30.6)	36 (41.4)	0.141
Neuropathy	81 (47.1)	38 (44.7)	43 (49.4)	0.535
Fontaine classification				
Stage III	48 (27.9)	20 (23.5)	28 (32.2)	0.206
Stage IV	124 (72.1)	65 (76.5)	59 (67.8)	
hsCRP (mg/L)	4.03 ± 5.96	4.32 ± 6.1	3.75 ± 5.84	0.528
HbA1c (%)	7.65 ± 1.56	7.58 ± 1.79	7.71 ± 1.34	0.591
Concomitant medications				
OHA alone	65 (37.8)	27 (31.8)	38 (43.7)	0.107
Insulin alone	78 (45.3)	43 (50.6)	35 (40.2)	0.172
Insulin duration, years	4.24 ± 3.9	4.4 ± 3.7	4.1 ± 4.1	0.576

BMI body mass index, *SBP* systolic blood pressure, *CAD* coronary artery disease, *DM* diabetes mellitus, *ESRD* end-stage renal disease, *CVA* cerebrovascular accident, ABI ankle brachial index, hsCRP high-sensitivity C-reactive protein, *HbA1c* hemoglobin A1c, *OHA* oral hypoglycemic agent

cilostazol group had ESRD (P = 0.775), cellulitis (P = 0.157), retinopathy (P = 0.141), neuropathy (P = 0.535), Fontaine stage IV CLI (P = 0.206), sole use of an oral hypoglycemic agent (OHA) (P = 0.107), and insulin use alone (P = 0.172), respectively. The mean level of

high-sensitivity C-reactive protein (hsCRP) was
4.32 ± 6.1 and 3.75 ± 5.84 in the control and
cilostazol groups, respectively ($P = 0.528$). No
significant difference was noted with regard to
the hemoglobin A1c (HbA1c) value in the con-
trol and cilostazol groups ($P = 0.591$).

All diseased arteries were characterized using
pretreatment imaging results on the basis of the
stratification of lesions as per the updated 2015
TASC II classification for aortoiliac, femor-
opopliteal, and infrapopliteal lesions. As pre-
sented in Table 2, the patients in the cilostazol
and control groups had multiple lesions. There
were no significant differences with regards to
aortoiliac, femoropopliteal, and infrapopliteal
lesions between the two groups.

Data on the baseline demographic and clin-
ical characteristics of the patients associated
with amputation are summarized in Supple-
mentary Table 1. The mean ages of the patients
in the no LEA (NLEA) and LEA groups were
74.9 ± 9.4 and 71.5 ± 9.5 years, respectively
($P = 0.018$); 51.6% (48), 77.4% (72), 44.1% (41),
63.4% (59), 96.8% (90), 21.5% (20), and 59.1%
(55) of the patients in the LEA group had ESRD
($P = 0.008$), cellulitis ($P < 0.001$), retinopathy
($P = 0.017$), neuropathy ($P < 0.001$), Fontaine
stage IV CLI ($P < 0.001$), OHA use alone
($P < 0.001$), and insulin use alone ($P < 0.001$),
respectively. The mean level of hsCRP was
1.96 ± 3.14 and 5.79 ± 7.13 in the NLEA and
LEA groups, respectively ($P < 0.001$). The mean
level of HbA1c was 7.48 ± 1.49 and 7.78 ± 1.61
in the NLEA and LEA groups, respectively
($P = 0.215$).

Endpoints

The associations of the duration of cilostazol
treatment with study endpoints at 24 months
for all participants and subgroups are summa-
rized in Table 3. In this study, 58 (33.7%) and

Table 2 Summary of lesion characteristics and distribution of diseased vessels in patients receiving cilostazol treatment for at most 3 months and more than 3 months

Lesion characteristics TASC II classification	Control group ($n = 85$)	Cilostazol group ($n = 87$)	P value
Aortoiliac lesions			0.337
A	13 (15.3)	12 (13.8)	
B	34 (40)	26 (29.9)	
C	7 (8.2)	6 (6.9)	
D	0 (0)	2 (2.3)	
Femoropopliteal lesions			0.333
A	6 (7.1)	2 (2.3)	
B	15 (17.6)	22 (25.3)	
C	42 (49.4)	43 (49.4)	
D	22 (25.9)	20 (23)	
Infrapopliteal lesions			0.665
B	17 (20)	22 (25.3)	
C	40 (47.1)	36 (41.4)	
D	28 (32.9)	29 (33.3)	

TASC Trans-Atlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease

Table 3 Cilostazol Associations of cilostazol treatment for at most 3 months and more than 3 months with study endpoints at 24 months

Parameters	Total population (n = 172)	Control group (n = 85)	Cilostazol group (n = 87)	P value
Successful interventions	172 (100)	85 (100)	87 (100)	
Simple angioplasty	58 (33.7)	30 (35.3)	28 (32.2)	
Stent implantation	114 (66.3)	55 (64.7)	59 (67.8)	0.666
Direct revascularization	129 (75)	59 (69.4)	70 (80.5)	0.094
Indirect revascularization	43 (25)	26 (30.6)	17 (19.5)	
Post-intervention ABI				
1 month		0.91 ± 0.1	0.95 ± 0.16	0.103
6 months		0.82 ± 0.18	0.94 ± 0.22	< 0.001
Primary patency				
6 months	148 (88.6)	67 (82.7)	81 (94.2)	0.02
12 months	120 (71.9)	44 (54.3)	76 (88.4)	< 0.001
18 months	90 (53.9)	21 (25.9)	69 (80.2)	< 0.001
24 months	83 (49.7)	15 (18.5)	68 (79.1)	< 0.001
Secondary patency				
12 months	133 (77.3)	51 (60)	82 (94.3)	< 0.001
24 months	109 (63.4)	36 (42.4)	73 (83.9)	< 0.001
AFSR at 24 months	79 (45.9)	31 (36.5)	48 (55.2)	0.014
LEA at 24 months	93 (54.1)	54 (63.5)	39 (44.8)	
Major	13 (7.6)	13 (15.3)	0	
Minor	80 (46.5)	41 (48.2)	39 (44.8)	
24-month mortality	19 (11)	14 (16.5)	5 (5.7)	0.029
24-month survival	153 (89)	71 (83.5)	82 (94.3)	0.029
12-month CAD events	35 (20.3)	15 (17.6)	20 (23.0)	0.384
24-month CAD events	72 (41.9)	30 (35.3)	42 (48.3)	0.084
12-month CVA events	11 (6.4)	4 (4.7)	7 (8.0)	0.535
24-month CVA events	16 (9.5)	8 (9.8)	8 (9.3)	0.92

ABI ankle brachial index, *AFSR* amputation-free survival rate, *LEA* lower-extremity amputation, *CAD* coronary artery disease, *CVA* cerebrovascular accident

114 (66.3%) of the 172 participants underwent angioplasty alone and angioplasty plus stent implantation, respectively. The two methods yielded no significant differences according to cilostazol subgroup analysis (P = 0.666). The two groups had comparable post-intervention

ABI scores at 1 month ($P = 0.103$), whereas the patients in the cilostazol group had a better post-intervention ABI at 6 months ($P < 0.001$).

The overall primary patency rates of the patients were 88.6% (148), 71.9% (120), 53.9% (90), and 59.7% (83) at 6, 12, 18, and 24 months, respectively. However, in the cilostazol subgroup analysis, significant differences were observed in the primary patency rate between the two groups at 6, 12, 18, and 24 months ($P = 0.02$, $P < 0.001$, $P < 0.001$, and $P < 0.001$, respectively). The secondary patency was better in the cilostazol group at 12 and 24 months ($P < 0.001$ and $P < 0.001$, respectively). The Kaplan–Meier curves for the time-to-primary cumulative patency analysis showed that the patients who received cilostazol treatment for more than 3 months had a better survival rate than the patients who received treatment for at most 3 months (log rank test, $P < 0.001$; Fig. 2). The overall amputation-free survival rate was 45.9% (79/172), and the percentage of amputations was significantly lower

in the cilostazol group than in the control group ($P = 0.014$). The 24-month overall survival (OS) rate was 89% (153), and there was a significant difference between the control and cilostazol groups ($P = 0.029$). In addition, 20.3% ($n = 35$) and 41.9% ($n = 72$) of the patients experienced CAD events at 12 and 24 months, respectively. No significant differences were detected in the occurrence of CAD at 12 and 24 months ($P = 0.384$ and $P = 0.084$) between the control and cilostazol groups. Eleven and 16 CVA events were observed at 12 and 24 months, and no significant differences were observed with regards to CVA at 12 and 24 months between the two groups. Nineteen patients died during the 24-month follow-up period. Of these, nine patients died of cardiogenic shock related to ischemic heart disease and seven patients died owing to sepsis as a result of diabetes-related foot complications. The remaining three uremic patients died of complications of major surgery and sepsis related to pneumonia.

The treatment methods and study endpoints associated with amputation at 24 months for all participants and subgroups are summarized in Supplementary Table 2. Thus, 28 (30.1%) and 65 (69.9%) patients in the LEA group underwent angioplasty alone and angioplasty plus stent implantation, respectively. The two methods yielded no significant difference in LEA subgroup analysis ($P = 0.277$). A higher percentage of patients in the NLEA group had DR than in the LEA group ($P = 0.017$). In the LEA subgroup analysis, significant differences were observed in the primary patency rate between patients who did and did not undergo LEA at 12, 18, and 24 months ($P = 0.011$, $P = 0.001$, and $P = 0.014$, respectively). The secondary patency was better in the patients without amputation at 12 months ($P < 0.001$). A total of 23.7% ($n = 22$) and 49.5% ($n = 46$) of the LEA group experienced CAD at 12 and 24 months, respectively. A significant difference in the occurrence of a CAD event at 24 months ($P = 0.028$) between the patients who did and did not undergo amputation was noted. No significant difference was observed in CVA between the two groups at 12 and 24 months. In total, 19 patients died during the 24-month follow-up period, 15 of whom had undergone
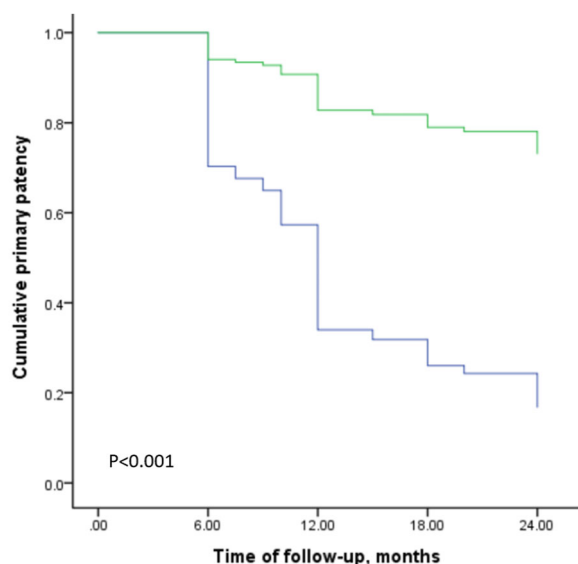
Number of patients at risk

≤ 3 M	85	67	44	21	15
> 3 M	87	81	76	69	68

Fig. 2 Patients who received cilostazol treatment for more than 3 months had a better patency rate than patients who received treatment for at most 3 months (log rank test, $P < 0.001$)

LEA ($P = 0.027$). After the intervention and multidisciplinary management, the outcomes of tissue loss were followed up, including major amputations (13), minor amputations (80), and wound-healing (34).

Assessment of Primary Patency

In the univariate Cox regression analysis of the 24-month primary patency, long-term cilostazol usage (HR 0.18, 95% CI 0.11–0.3, $P < 0.001$), cellulitis (yes/no) (HR 1.86, 95% CI 1.12–3.08, $P = 0.016$), OHA use alone (HR 0.63, 95% CI 0.39–1.0, $P = 0.051$), duration of insulin use (HR 1.06, 95% CI 1.0–1.13, $P = 0.045$), DR (HR 0.42, 95% CI 0.27–0.66, $P < 0.001$), and exercise (HR 0.3, 95% CI 0.19–0.46, $P < 0.001$) were significantly associated with primary patency at 24 months (Table 4). Furthermore, the results of a weighted multivariate Cox regression model with the ATE showed that three main factors were independently associated with the 24-month primary patency: cilostazol treatment for more than 3 months (HR 0.2, 95% CI 0.11–0.36, $P < 0.001$), DR (HR 0.46, 95% CI 0.28–0.74, $P = 0.002$), and exercise (HR 0.4, 95% CI 0.24–0.66, $P < 0.001$; Table 4).

Assessment of Amputation

Univariate Cox regression analysis was first conducted to identify the clinical variables associated with amputation (Table 5). The following clinical factors were found to be associated with a relatively higher risk of LEA: cellulitis (HR 3.24, 95% CI 1.99–5.28, $P < 0.001$), DM retinopathy (HR 1.59, 95% CI 1.05–2.4, $P = 0.027$), neuropathy (HR 2.32, 95% CI 1.51–3.55, $P < 0.001$), cilostazol treatment (> 3 months/≤ 3 months) (HR 0.67, 95% CI 0.45–1.02, $P = 0.006$), insulin use alone (HR 2.08, 95% CI 1.37–3.16, $P < 0.001$), OHA use alone (HR 0.36, 95% CI 0.22–0.59, $P < 0.001$), duration of insulin treatment (HR 1.12, 95% CI 1.06–1.18, $P < 0.001$), and no supervised exercise (HR 2.21, 95% CI 1.46–3.34, $P < 0.001$). Moreover, the significant and potential factors were analyzed using a weighted Cox regression model with the ATE method. Finally, cellulitis

and neuropathy were found to be independently associated with amputation (cellulitis: HR 2.89, 95% CI 1.66–5.05, $P < 0.001$; neuropathy: HR 2.2, 95% CI 1.31–3.7, $P = 0.003$).

DISCUSSION

Treatment of diabetic CLI is more challenging as compared with treatment of proximal PAOD with claudication as a result of multiple risk factors in patients and diffuse tough calcification in infrapopliteal lesions. Despite great advances in surgical and endovascular techniques, the clinical outcome of CLI in patients with DM is still inconsistent. This study demonstrated that cilostazol treatment for more than 3 months combined with a multidisciplinary approach may improve the clinical outcome and prevent further tissue loss in patients with DM and CLI after endovascular revascularization of the affected angiosome.

Cilostazol is a selective inhibitor of phosphodiesterase type 3 (PDE III inhibitor). It has a therapeutic focus on the inhibition of phosphodiesterase activity and suppression of cAMP degradation, resulting in increased cAMP in platelets and blood vessels and leading to inhibition of platelet aggregation and vasodilation [34]. Cilostazol is indicated for the treatment of intermittent claudication in patients with PAOD [35, 36]. In recent years, cilostazol has been used for the secondary prevention of brain infarction through its antiplatelet antithrombotic effects [37]. Furthermore, some studies have shown that cilostazol can prevent the proliferation of smooth muscle cells, consequently increasing peripheral blood flow and insulin sensitivity by reducing inflammation [35, 38]. However, insufficient data are available to explain whether cilostazol increases the functional status of the involved lower extremities, improves primary patency in patients with CLI, as well as subsequent improvement in quality of life, and reduces the occurrence of adverse cardiovascular events and all-cause mortality. This study comprehensively demonstrated that cilostazol treatment for more than 3 months improved

Table 4 Cox regression analysis of primary patency

Variable	Univariate		Multivariate[a]	
	HR (95% CI)	*P* value	ATE HR (95% CI)	ATT HR (95% CI)
Age, years	1.0 (0.98–1.03)	0.697		
Gender (F/M)	1.51 (0.99–2.32)	0.059	0.93 (0.57–1.54)	0.98 (0.59–1.65)
BMI	0.99 (0.94–1.05)	0.775		
Smoking (yes/no)	1.12 (0.72–1.73)	0.615		
Hyperlipidemia (yes/no)	1.45 (0.94–2.23)	0.095	1.35 (0.85–2.16)	1.43 (0.89–2.3)
CAD (yes/no)	0.94 (0.6–1.46)	0.766		
Hypertension (yes/no)	0.8 (0.52–1.67)	0.803		
ESRD (yes/no)	0.98 (0.64–152)	0.942		
Calcification (yes/no)	1.4 (0.92–2.15)	0.118	1.25 (0.75–2.07)	1.14 (0.67–1.92)
Fontaine stage (IV/III)	1.28 (0.78–2.09)	0.329		
Cellulitis (yes/no)	1.86 (1.12–3.08)	0.016	1.18 (0.72–1.94)	1.18 (0.71–1.96)
Neuropathy	1.11 (0.72–1.69)	0.64		
Ischemia severity	1.26 (0.78–2.02)	0.341		
ABI < 0.6/ABI ≥ 0.6				
Statin (yes/no)	1.25 (0.81–1.93)	0.304		
Antiplatelet (yes/no)	0.99 (0.53–1.87)	0.991		
Cilostazol (> 3 months/≤ 3 months)	0.18 (0.11–0.3)	< 0.001	0.2 (0.11–0.36)	0.21 (0.11–0.38)
Insulin alone (yes/no)	1.42 (0.93–2.17)	0.11	0.80 (0.39–1.66)	0.79 (0.37–1.69)
OHA alone (yes/no)	0.63 (0.39–1.0)	0.051	0.98 (0.31–3.09)	0.88 (0.26–2.94)
Duration of insulin, years	1.06 (1.0–1.13)	0.045	0.98 (0.89–1.09)	0.98 (0.88–1.08)
Involved leg (L/R)	0.8 (0.53–1.23)	0.313		
Intervention (PTA/stenting)	0.83 (0.52–1.33)	0.44		
DR/IR	0.42 (0.27–0.66)	< 0.001	0.46 (0.28–0.74)	0.41 (0.28–0.75)
Exercise (yes/no)	0.3 (0.19–0.46)	< 0.001	0.4 (0.24–0.66)	0.41 (0.24–0.68)

HR hazard ratio, *CI* confidence interval, *BMI* body mass index, *CAD* coronary artery disease, *DM* diabetes mellitus, *ESRD* end-stage renal disease, *DR* direct revascularization, IR indirect revascularization, *PTA* percutaneous transluminal angioplasty, *ABI* ankle brachial index, *OHA* oral hypoglycemic agent

[a] Multivariate weighted Cox regression with average treatment effect (ATE) or average treatment effect on the treated (ATT)

the 6-, 12-, 18-, and 24-month primary patency, subsequently promoting wound-healing and decreasing the risk of LEA as compared with cilostazol treatment for at most 3 months. Notably, recent studies reporting that cilostazol treatment may improve stent patency in

Table 5 Cox regression analysis of risk factors associated with amputation

Variable	Univariate		Multivariate[a]	
	HR (95% CI)	*P* value	ATE	ATT
Age, years	0.98 (0.96–1.0)	0.076	0.99 (0.97–1.01)	0.99 (0.97–1.02)
Gender (F/M)	1.17 (0.77–1.78)	0.457		
BMI	0.99 (0.94–1.04)	0.681		
Smoking (yes/no)	1.04 (0.68–1.59)	0.852		
Hyperlipidemia (yes/no)	1.0 (0.66–1.5)	0.988		
Baseline CAD (yes/no)	0.69 (0.45–1.07)	0.097	0.8 (0.52–1.23)	0.78 (0.5–1.22)
Hypertension (yes/no)	0.67 (0.39–1.16)	0.155		
ESRD (yes/no)	1.41 (0.94–2.11)	0.1	0.83 (0.53–1.3)	0.82 (0.52–1.3)
Cellulitis (yes/no)	3.24 (1.99–5.28)	< 0.001	2.89 (1.66–5.05)	2.98 (1.69–5.25)
Retinopathy (yes/no)	1.59 (1.05–2.4)	0.027	1.36 (0.8–2.32)	1.44 (0.84–2.48)
Neuropathy (yes/no)	2.32 (1.51–3.55)	< 0.001	2.2 (1.31–3.7)	2.29 (1.36–3.84)
Calcification (yes/no)	1.24 (0.81–1.91)	0.324		
Ischemia severity	1.11 (0.72–1.7)	0.643		
ABI < 0.6/ABI ≥ 0.6				
Interventions	0.84 (0.54–1.31)	0.434		
(PTA/stent)				
IR/DR	1.51 (0.98–2.34)	0.063	1.25 (0.82–1.9)	1.14 (0.75–1.74)
Statin (yes/no)	0.93 (0.62–1.39)	0.71		
Antiplatelet (yes/no)	0.83 (0.45–1.52)	0.548		
Cilostazol (> 3 months/≤ 3 months)	0.67 (0.45–1.02)	0.006	0.78 (0.49–1.24)	0.77 (0.49–1.23)
Insulin alone (yes/no)	2.08 (1.37–3.16)	< 0.001	0.81 (0.46–1.4)	0.73 (0.42–1.26)
OHA alone (yes/no)	0.36 (0.22–0.59)	< 0.001	0.59 (0.22–1.59)	0.56 (0.21–1.51)
Insulin duration, years	1.12 (1.06–1.18)	< 0.001	1.05 (0.95–1.17)	1.05 (0.95–1.16)
Exercise (no/yes)	2.21 (1.46–3.34)	< 0.001	0.99 (0.56–1.74)	1.01 (0.57–1.78)
Involved leg (L/R)	0.91 (0.61–1.37)	0.651		

HR hazard ratio, *CI* confidence interval. *BMI* body mass index, *CAD* coronary artery disease, *DM* diabetes mellitus, *ESRD* end-stage renal disease, *DR* direct revascularization, *IR* indirect revascularization, *PTA* percutaneous transluminal angioplasty, *ABI* ankle brachial index, *OHA* oral hypoglycemic agent
[a] Multivariate weighted Cox regression with average treatment effect (ATE) or average treatment effect on the treated (ATT)

coronary or peripheral arteries [16, 17, 19] were in accordance with our preliminary findings; that is, cilostazol treatment can improve the primary patency and further decrease the LEA and mortality rates in patients with CLI and DM.

Another concern was the role of supervised exercise in patients with CLI and DM. Numerous studies have indicated that exercise rehabilitation improves the functional outcomes and peripheral circulation of patients with PAOD presenting with intermittent claudication [39, 40]. The 2016 ACC/AHA guidelines state that exercise plays a key role in the treatment of claudication, with substantial improvements reported in functional status [41]. This guideline supported our results that a supervised exercise program was an independent factor influencing the 24-month primary patency, which consequently may have decreased the LEA risk in patients with DM and CLI (Fig. 2, Table 3, and Supplementary Tables 1 and 2).

Another concern was revascularization based on the angiosome concept. Some studies have shown that the improvements of wound-healing and the major amputation rate after IR in the presence of collaterals were similar to the outcomes after DR in patients with CLI [16, 17, 19, 42]. Accordingly, our results indicated that DR based on the affected angiosome is an important factor affecting the primary patency and decreasing the risk of LEA.

People with DM and CLI are susceptible to foot problems, manifested as several characteristic pathologies such as infection, neuropathy, diabetic foot ulcer, ischemic pain, and gangrene change, which cause poor blood circulation to the lower limb, finally leading to amputation. Some studies have reported that CLI combined with diabetic foot ulcer is a major cause of morbidity, accounting for approximately two-thirds of all non-traumatic amputations performed in the USA [43, 44]. The causes of amputations are multifactorial, and diabetic neuropathy and cellulitis were independent predisposing factors associated with the risk of LEA according to the results of weighted multivariate Cox analysis. Diabetic neuropathy is nerve damage or dysfunction, frequently resulting from poor control of a high sugar level and subsequent impairment of microcirculation. Nerve damage usually decreases the peripheral sensation in the lower limbs, which can cause unnoticed injuries of the foot, manifested with skin ulcers or infections. In this study, of the 81 patients with diabetic neuropathy, 72.8% (59) had LEAs ($P < 0.001$, Supplementary Table 1). Neuropathy, intractable infection, and severe PAOD may compromise microcirculation and macrocirculation of the lower limbs, breaking down the tissue and finally leading to amputation.

The results obtained after a 24-month follow-up period demonstrated that 93 (54.1%) patients required LEA, with 80 (46.5%) requiring minor amputation and 13 (7.6%) requiring major amputation. The rate of major LEA in this study was considerably lower than the corresponding rate observed in some previous trials [43–45]. Furthermore, during the 24-month follow-up period, the risk of LEA was highly associated with newly developed ischemic heart disease, with 49.5% ($n = 46$) of the patients who underwent LEA developing this disease as compared with 32.9% ($n = 26$) of the patients who did not undergo LEA ($P = 0.028$). The mortality rate of the patients who underwent LEA was 16.1% ($n = 15$), as compared with a mortality rate of 5.1% ($n = 4$) in the patients who did not undergo LEA ($P = 0.027$). The patients with DM who underwent LEA had a 1.5-fold and 3-fold higher risk of new CAD events and mortality events, respectively, as compared with the patients who did not undergo LEA. These results indicated that amputation is a lethal medical condition, and that patients undergoing LEA experience markedly more cardiovascular events and have a higher mortality rate than patients who do not undergo LEA. Therefore, prevention of diabetic foot ulcer is a key measure; aggressive treatment of diabetic foot ulcers is challenging and prolonged and requires a multidisciplinary team and multiple approaches to preserve limb function, decrease cardiovascular complications, and promote quality of life [45, 46].

Patients with insulin resistance or poor control of their sugar level are more likely to develop microvascular complications (including retinopathy, neuropathy, kidney failure, and diabetic foot), and later macrovascular complications (such as stroke, cardiovascular disease, and heart failure). In this study, we found that over half of LEAs were attributable to a combination of DM, neuropathy,

calcification, cellulitis and ESRD. DM is a chronic illness that causes endothelial and platelet dysfunction. In particular, DM combined with CKD is a leading cause of vascular calcification (VC), particularly medial arterial calcification (Mönckeberg's medial sclerosis). Numerous studies have proposed that VC is most common in patients with DM and CKD, and that it is associated with increased cardiovascular morbidity and mortality [45, 47–50].

According to subgroup analysis, 73 (42.4%) and 75 (43.6%) patients with DM had ESRD and calcification of the involved arteries, respectively, and 31 of 43 patients with ESRD and calcification had undergone LEA ($P = 0.006$, Supplementary Table 1). These novel findings indicated that arterial calcification is associated with the risk of LEA in patients with DM undergoing dialysis. Owing to the small size of the calcification subgroup, further studies are warranted to verify the associations of arterial calcification with cardiovascular and LEA risks.

This study had some potential limitations that should be addressed. The first limitation was that it was a non-randomized study that did not provide sufficient power for extensive statistical comparisons. To decrease the bias, a PS-weighted multivariate Cox regression model was used to evaluate the associations with primary patency and amputation based on disease severity and location. The second limitation was the small number of patients with DM and CLI owing to the strict inclusion criteria that all patients must have received cilostazol treatment after successful revascularization. The third limitation was that the reports of subgroup analyses were not head-to-head or matched comparisons. More longitudinal, comparative clinical trials should be conducted with larger sample sizes to further investigate the relative outcomes and mortality in patients with DM and CLI.

CONCLUSION

Patients with DM who received cilostazol treatment for more than 3 months had significantly better outcomes and decreased amputation rates after direct revascularization of the affected angiosome. Furthermore, cellulitis and diabetic neuropathy were the main predisposing factors for the occurrence of LEA. Future longitudinal and comparative clinical trials should be conducted with larger sample sizes to further investigate the associations of cilostazol treatment with the relative outcomes and mortality in patients with DM and CLI.

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