Original Research

Association Between Hemodynamic Improvement and Functional Outcomes Following Endovascular Revascularization and Adjunctive Prostaglandin E1 Therapy in Chronic Limb-Threatening Ischemia: A Retrospective Cohort Study

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Abstract

Introduction: Chronic limb-threatening ischemia (CLTI) is the most severe form of peripheral arterial disease, with substantial risks of limb loss and impaired quality of life. This study evaluated the association between hemodynamic improvement after endovascular revascularization and clinical outcomes, including the potential adjunctive effect of prostaglandin E1 (PGE1). **Materials and Methods:** This retrospective cohort study included 60 patients with CLTI who underwent tibial angioplasty. Baseline and 6-month outcomes were compared. Hemodynamic parameters included ankle-brachial index (ABI) and toe pressure, while clinical outcomes included pain, ulcer healing, limb salvage, and vessel patency. Statistical analyses included parametric/nonparametric tests, correlation, and mediation analysis. **Results:** Mean ABI increased from 0.38 ± 0.12 to 0.71 ± 0.09 ($P < .001$), while median toe pressure increased from 25 to 48 mm Hg ($P < .001$). Mean visual analog scale pain score decreased from 7.4 ± 1.3 to 2.9 ± 1.2. Among 33 patients with ulcers, 25 (75.8%) achieved complete healing, with a median healing time of 84 days. Limb salvage was achieved in 53 (88.3%) patients. ABI improvement correlated with pain reduction ($P = -.58$) and shorter ulcer healing time ($P = -.48$). PGE1 therapy was associated with greater ABI improvement and higher ulcer healing rates. **Conclusion:** Hemodynamic improvement after revascularization was associated with better clinical outcomes in CLTI. Adjunctive PGE1 therapy was associated with greater perfusion improvement and ulcer healing. Given the small sample and retrospective, nonrandomized design, these are exploratory associations only; causality cannot be established, and the mediation findings are not interpreted as beneficial effects or independent benefits of PGE1.

J CRIT LIMB ISCHEM 2026;6(4):E136-E144. doi: 10.25270/jcli/CLIG-2600016

Key words: ankle-brachial index, chronic limb-threatening ischemia, endovascular revascularization, limb salvage, prostaglandin E1

Introduction

Chronic limb-threatening ischemia (CLTI) is the most advanced stage of peripheral arterial disease and is associated with substantial morbidity, impaired quality of life, and a high risk of limb loss. It is clinically characterized by ischemic rest pain, nonhealing ulcers, or gangrene resulting from severely compromised arterial perfusion. With the rising prevalence of diabetes mellitus, hypertension, and atherosclerotic risk factors, the burden of CLTI continues to increase, particularly in low- and middle-income countries.[1,2] Timely restoration of blood flow is essential for relieving symptoms, promoting tissue healing, and preventing major amputations. Contemporary international guidelines, including the International Working Group on the Diabetic Foot guidelines, emphasize the critical importance of timely revascularization combined with optimized wound care and off-loading strategies to improve ulcer healing and reduce amputation risk in patients with diabetic foot disease and CLTI.[3]

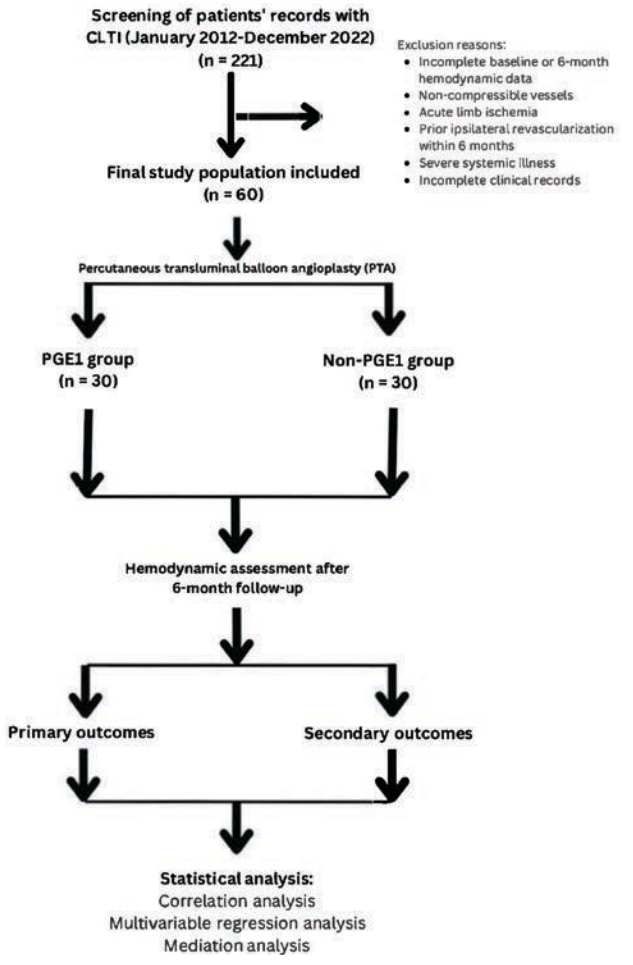

FIGURE. Study flowchart.

Endovascular revascularization, particularly percutaneous transluminal angioplasty of the infrapopliteal vessels, has emerged as a cornerstone in the management of CLTI because of its minimally invasive nature and favorable safety profile.[4] Restoration of macrovascular patency through angioplasty is expected to improve distal blood flow, which can be objectively assessed using hemodynamic parameters such as the ankle-brachial index (ABI).[5,6] Improvement in hemodynamic parameters is generally assumed to translate into clinical benefits, including a reduction in ischemic pain and enhancement of wound healing. However, in clinical practice, the relationship between hemodynamic improvement and symptom relief is not always linear or predictable.[7]

Pain in CLTI is multifactorial and influenced not only by macrocirculatory blood flow but also microvascular dysfunction, tissue hypoxia, neuropathy, and inflammatory mediators. Consequently, some patients continue to experience significant pain despite technically successful revascularization, whereas others report rapid symptomatic improvement. This variability highlights the need to better understand the relationship between objective perfusion changes and subjective pain outcomes following endovascular interventions.[8,9]

The ABI is a widely used, noninvasive hemodynamic measure of lower limb perfusion and serves as an important indicator of treatment success after revascularization.[5,6] Similarly, pain severity is commonly assessed using validated scales, such as the visual analog scale (VAS), which provides a quantitative measure of patient-reported outcomes.[10] Evaluating the association between changes in ABI and corresponding changes in VAS scores may provide valuable insights into the extent to which hemodynamic improvement translates into symptomatic benefits.

In addition, adjunctive therapies such as prostaglandin E1 (PGE1), which possesses vasodilatory and microcirculatory effects, are sometimes administered as part of routine clinical care following angioplasty.[11,12] While such therapies may influence hemodynamic parameters and symptom outcomes, their role in modifying the relationship between hemodynamic improvement and pain relief remains unclear. Therefore, the present retrospective cohort study aimed to evaluate the association between hemodynamic improvement and functional outcomes, including pain reduction and ambulatory capacity, in patients who underwent endovascular revascularization for CLTI. This study also sought to explore the clinical and treatment-related factors that may influence functional recovery following intervention.

Materials and Methods

Study design and ethical considerations

This retrospective cohort study was conducted in the Department of Vascular Surgery, Vascular Care Center, Hyderabad, India using archived patient records spanning a 10-year period (January 2012-December 2022). This study was based exclusively on previously recorded clinical data retrieved from the medical records. As the analysis involved a retrospective review of existing anonymized patient records with no direct patient interaction or intervention, formal ethical approval and individual patient consent were not required.

Study population

A total of 221 patients treated for CLTI were screened, of whom 60 patients with CLTI secondary to infrapopliteal arterial disease met the inclusion criteria and were included in the study. Eligible patients were aged between 40 and 80 years and presented with ischemic rest pain, nonhealing ulcers, or gangrene, with angiographic evidence of tibial vessel disease amenable to intervention. Only patients who underwent technically successful endovascular revascularization and had complete baseline and 6-month follow-up data were included in the study (**Figure**). All included patients had infrapopliteal (tibial) arterial disease as the primary target for revascularization. Multilevel disease involving the femoropopliteal segment was present in a subset of patients and treated as necessary to ensure adequate inflow; however, the index procedure analyzed in this study was tibial angioplasty.

Table 1. Baseline demographic and clinical characteristics of the study population (n = 60)

Parameter	Total (n = 60)	PGE1 group (n = 30)	Non-PGE1 group (n = 30)	*P* value
Demographics				
Age (years), mean ± SD	68.4 ± 8.2	67.8 ± 8.5	69.1 ± 7.9	.52
Male sex, n (%)	39 (65.0)	21 (70.0)	18 (60.0)	.42
Comorbidities				
Diabetes mellitus, n (%)	39 (65.0)	21 (70.0)	18 (60.0)	.42
Hypertension, n (%)	51 (85.0)	26 (86.7)	25 (83.3)	.72
Dyslipidemia, n (%)	36 (60.0)	19 (63.3)	17 (56.7)	.60
Current/past smoking, n (%)	48 (80.0)	25 (83.3)	23 (76.7)	.52
Ischemic heart disease, n (%)	27 (45.0)	15 (50.0)	12 (40.0)	.43
CKD (eGFR < 60), n (%)	18 (30.0)	10 (33.3)	8 (26.7)	.57
Clinical presentation				
Ischemic rest pain, n (%)	27 (45.0)	12 (40.0)	15 (50.0)	.43
Ulceration, n (%)	24 (40.0)	14 (46.7)	10 (33.3)	.29
Gangrene, n (%)	9 (15.0)	4 (13.3)	5 (16.7)	.72
Duration of symptoms (months), median (IQR)	8 (4-14)	7 (4-12)	9 (5-15)	.18
Hemodynamic parameters				
Baseline ABI, mean ± SD	0.38 ± 0.12	0.36 ± 0.11	0.40 ± 0.13	.21
Baseline toe pressure (mm Hg), median (IQR)	25 (18-32)	23 (16-30)	27 (20-34)	.09
Wound				
Ulcer present, n (%)	33 (55.0)	17 (56.7)	16 (53.3)	.80
Infection (mild/moderate), n (%)	29 (48.3)	15 (50.0)	14 (46.7)	.80
Treatment variables, n (%)				
PTA performed, n (%)	60 (100.0)	30 (50.0)	30 (50.0)	1.00
Tibial vessel targeted, n (%)	60 (100.0)	30 (50.0)	30 (50.0)	1.00
Adjunctive PGE1 therapy, n (%)	30 (50.0)	30 (50.0)	-	-
Antiplatelet use, n (%)	57 (95.0)	29 (96.7)	28 (93.3)	.55
Anticoagulant use, n (%)	24 (40.0)	12 (40.0)	12 (40.0)	1.00

Data are presented as mean ± SD, median (IQR), or frequency (percentage) as appropriate. Abbreviations: PGE1, prostaglandin E1; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ABI, ankle-brachial index; PTA, percutaneous transluminal angioplasty.

Patients were excluded if they had acute limb ischemia, prior ipsilateral revascularization within 6 months, noncompressible vessels, severe systemic illness precluding meaningful follow-up, or incomplete clinical records. Noncompressible vessels were defined as an ABI greater than 1.40 or when the ankle arteries could not be occluded at cuff pressures exceeding 250 mm Hg. The relatively modest final sample size reflects the strict requirement for complete hemodynamic and clinical data at both baseline and 6 months; many of the screened patients lacked standardized serial ABI/toe pressure measurements or complete wound-healing documentation and were therefore excluded. The total institutional volume of CLTI interventions during the same 10-year period was substantially higher, but only those cases meeting the above data-completeness criteria were retained for this retrospective analysis.

Procedural protocol

All patients underwent percutaneous transluminal balloon angioplasty of the tibial (infrapopliteal) vessels under local anesthesia.[13] The intervention consisted of balloon angioplasty; atherectomy devices were not used. Provisional stenting (bare-metal or drug-eluting) was performed only for flow-limiting dissection or residual stenosis greater than 30% that could not be corrected by prolonged balloon inflation and was required in a minority of cases. Vascular access was obtained via the common femoral artery, followed by lesion crossing and balloon angioplasty. Technical success was defined as the restoration of antegrade blood flow with less than 30% residual stenosis.

Adjunctive intra-arterial PGE1 therapy was administered to 30 patients (50%) at the discretion of the treating physician according to institutional protocols. Selection was generally guided by the presence of extensive tissue loss, poor runoff, or residual ischemic symptoms after angioplasty; however, no formal standardized criteria or randomization was applied. PGE1 was typically given as an intra-arterial infusion of 20 to 40 μg over 20 to 30 minutes immediately after successful angioplasty (exact dosing and duration varied by operator and were recorded in the procedural notes).

Postprocedural management included antiplatelet therapy in 57 patients (95%) and anticoagulant therapy in 24 patients (40%), along with optimization of comorbid conditions. Dual antiplatelet therapy was used in the majority of cases for at

TABLE 2. COMPARISON OF CLINICAL AND HEMODYNAMIC OUTCOMES AT BASELINE AND 6-MONTH FOLLOW-UP (n = 60)

Outcome measure	Baseline	6 months	Test statistic	*P* value
Hemodynamic outcomes				
ABI (Mean ± SD)	0.38 ± 0.12	0.71 ± 0.09	t = −18.42	< .001*
Toe pressure (mm Hg), median (IQR)	25 (18-32)	48 (38-56)	Z = −6.71	< .001*
Pain outcome				
VAS score (mean ± SD)	7.40 ± 1.30	2.90 ± 1.20	t = 20.11	< .001*
Wound/ulcer outcomes (n = 33 with ulcers)				
Ulcer healed, n (%)	0 (0)	25 (75.8)	χ^2 = 38.18	< .001*
Time to ulcer healing (days), median (IQR)	—	84 (63-112)	—	—
Vessel and limb outcomes (n = 60)				
Vessel patency at 6 months, n (%)	—	47 (78.3)	—	—
Limb salvage, n (%)	60 (100)	53 (88.3)	χ^2 (McNemar) = 9.33	.002*
Major amputation, n (%)	0 (0)	7 (11.7)	—	—

Data are presented as mean ± SD, median (IQR), or frequency (percentage) as appropriate. Paired t-test was used for normally distributed continuous variables, and Wilcoxon signed-rank test was used for non-normally distributed variables. McNemar chi-square test was used for paired categorical variables. Normality was assessed using the Shapiro–Wilk test. *P < .05 was considered statistically significant. A dash (—) indicates data not applicable for that variable. Abbreviations: ABI, ankle-brachial index; VAS: visual analog scale.

least 1 to 3 months, after which most patients were continued on long-term single antiplatelet therapy with aspirin or clopidogrel according to physician preference and bleeding risk. Post-procedural anticoagulant therapy was used at the discretion of the treating physician, typically when an independent indication existed (such as atrial fibrillation) or when the residual thrombotic risk after complex tibial intervention was judged to be high; no standardized institutional algorithm was applied during the study period.

Lesion characteristics were assessed on pre-procedural angiography. All patients had infrapopliteal (tibial) disease as the primary target for revascularization. Isolated single-vessel tibial disease was uncommon; the majority had multilevel tibial involvement. Multilevel disease involving the femoropopliteal segment was present in a subset of patients and was treated as necessary to ensure adequate inflow before or during the tibial intervention.

Target-vessel runoff was classified angiographically as good (direct inline flow to the foot), intermediate, or poor. Direct (angiosome-oriented) revascularization of the artery supplying the wound was attempted whenever anatomically feasible; when this could not be achieved, indirect revascularization via collaterals was accepted. Technical success was defined as residual stenosis 30% with restoration of antegrade flow. Detailed quantitative data on lesion length, calcification severity, and exact number of runoff vessels were not systematically recorded in a structured database for all cases and therefore could not be included in the multivariable models.

Clinical and hemodynamic assessment

Baseline data, including demographic characteristics, comorbidities, and clinical presentation, were recorded. The ABI was measured by trained vascular technologists or vascular surgery residents using a handheld continuous-wave Doppler device and a standard calibrated sphygmomanometer, following a uniform institutional protocol. Systolic pressures were obtained from the dorsalis pedis and posterior tibial arteries at the ankle and from the brachial artery in both arms. The ABI was calculated as the ratio of the higher ankle systolic pressure to the higher brachial systolic pressure. ABI values were interpreted as follows: normal (1.00-1.40), borderline (0.91-0.99), mild peripheral arterial disease (0.70-0.90), moderate disease (0.40-0.69), and severe ischemia (< 0.40). An increase in ABI following intervention was considered indicative of improved limb perfusion.[5,6] Hemodynamic parameters were assessed using the ABI and toe pressure measurements.[5,6] Pain severity was evaluated using a VAS.[10] Ulcer characteristics were documented, and wound healing was assessed using standardized clinical examinations and wound photography. Ulcer size reduction was measured in square centimeters (cm^2).

Wound care was provided according to institutional standards and coordinated with the treating vascular team. Ulcers were managed with regular sharp debridement, moist wound dressings, offloading when appropriate, and culture-directed antibiotics for clinically infected wounds. Negative-pressure wound therapy was used selectively for deeper wounds. No standardized wound care protocol or wound care specialist was mandated across the entire 10-year period; therefore, some variability in local wound management is acknowledged as a potential confounding factor.

Follow-up and outcome measures

Patients were followed up for 6 months, with assessments conducted at baseline and at the end of the follow-up period. The primary outcomes included hemodynamic improvement, defined as a change in ABI (ΔABI), and functional improvement, assessed by a change in the VAS score (ΔVAS). Hemodynamic improvement was defined as any increase in ABI from baseline. A clinically meaningful improvement was considered a ΔABI greater than or equal to 0.15, consistent with previous literature[14]; however,

Table 3. Correlation between hemodynamic improvement and functional outcomes (n = 60)

Correlation pair	Test used	r/ρ	*P* value	Interpretation
ΔABI vs ΔVAS	Spearman	ρ = −0.58	.001*	Moderate negative
ΔABI vs ulcer healing time (days)	Spearman	ρ = −0.48	.003*	Moderate negative
ΔABI vs major-event-free survival	Spearman	ρ = +0.36	.018*	Weak positive
ΔToe pressure vs ΔVAS	Spearman	ρ = −0.51	.002*	Moderate negative
ΔToe pressure vs ulcer healing time	Spearman	ρ = −0.45	.004*	Moderate negative
ΔABI vs limb salvage (binary)	Point-biserial	r = +0.44	.006*	Moderate positive

Data are presented as mean ± SD, median (IQR), or frequency (percentage) as appropriate Spearman correlation (ρ) was used for non-normally distributed data, and point-biserial correlation (r) was used for continuous vs binary variables. Δ indicates change from baseline to 6 months. Correlation strength was interpreted as weak (< 0.3), moderate (0.3-0.5), or strong (> 0.5), *P < .05 was considered statistically significant. ΔToe pressure (mm Hg) indicates the change in toe systolic pressure from baseline to 6 months. Major-event-free survival was defined as the absence of major amputation or death during the 6-month follow-up period and was analyzed as a binary outcome (yes/no). Abbreviations: ABI, ankle-brachial index; VAS, visual analog scale.

continuous ΔABI was used as the primary hemodynamic variable in correlation and regression analyses.

Secondary outcomes included ulcer healing status, time to ulcer healing, vessel patency, limb salvage, and the incidence of major amputation. Vessel patency at 6 months was assessed by duplex ultrasound (peak systolic velocity ratio < 2.5 and maintenance of antegrade flow) or by clinical examination combined with maintained hemodynamic improvement when duplex was not available. The primary focus of the analysis was the association between hemodynamic improvement and functional outcomes. Adjunctive PGE1 therapy was evaluated as an observed covariate rather than the main exposure variable.

Sample size estimation

The sample size was calculated using G*Power (version 3.1.9.7; Heinrich Heine University Düsseldorf). Based on prior evidence demonstrating a mean ABI improvement of 0.33 ± 0.10 following revascularization, a minimum sample size of 54 patients was required to achieve 80% statistical power at a 2-tailed significance level of 0.05 using a paired t-test.[14] This study was finally conducted on 60 records.

Statistical analysis

Statistical analyses were performed using SPSS Statistics (version 26.0; IBM Corp.). Continuous variables are expressed as mean ± SD or median with IQR, whereas categorical variables are presented as frequencies and percentages. The normality of the data distribution was assessed using the Shapiro-Wilk test. For normally distributed data, parametric tests, including paired sample t-test and independent samples t-test, were applied. Non-normally distributed data were analyzed using the Wilcoxon signed-rank test and Mann-Whitney U test. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. The correlation between hemodynamic and functional outcomes was evaluated using Spearman rank correlation coefficients. Point-biserial correlation was used to assess the associations between continuous and binary variables. Multivariable regression analysis was performed to assess the independent effect of PGE1 therapy on clinical outcomes after adjusting for potential confounders, including age, diabetes mellitus, baseline ABI, and lesion characteristics. Additionally, propensity score adjustment was employed to reduce the selection bias associated with treatment allocation. Mediation analysis was conducted using regression-based methods with bootstrapping (5000 resamples) to evaluate the indirect effects. A 2-sided P < .05 was considered statistically significant.

Results

Baseline characteristics (**Table 1**) showed that the cohort had a mean age of 68.4 ± 8.2 years with 39 (65%) men and 21 (35%) women. A high burden of comorbidities was observed, including diabetes in 39 (65%) and hypertension in 51 (85%). Most patients presented with ischemic rest pain in 27 (45%) or ulceration in 33 (55%), indicating advanced disease. Baseline perfusion was markedly reduced, with mean ABI of 0.38 ± 0.12 and median toe pressure of 25 mm Hg. Although the groups were broadly comparable, residual differences in lesion distribution or wound severity cannot be completely excluded and may have influenced the observed associations.

At 6-month follow-up (**Table 2**), there was a significant improvement in hemodynamic and clinical outcomes. Mean ABI increased to 0.71 ± 0.09 and toe pressure improved to 48 mm Hg. Pain scores decreased from 7.4 ± 1.3 to 2.9 ± 1.2. Among patients with ulcers, 25 (75.8%) achieved complete healing, with a median healing time of 84 days. Vessel patency was observed in 47 (78.3%) patients, while limb salvage was achieved in 53 (88.3%), with 7 (11.7%) patients undergoing major amputation.

Correlation analysis (**Table 3**) demonstrated significant associations between hemodynamic improvement and functional outcomes. Change in ABI showed a moderate negative correlation with change in pain (ρ = −0.58) and ulcer healing time (ρ = −0.48), and a positive correlation with limb salvage (r = 0.44). Improvements in toe pressure were also correlated with reduction in pain (ρ = −0.51) and faster healing (ρ = −0.45).

In an exploratory mediation analysis (**Table 4**), PGE1 use was associated with ulcer healing (total-association odds ratio [OR] = 3.80), and part of that association was statistically consistent with a pathway through ABI change (indirect OR = 1.19). PGE1 use

TABLE 4. MEDIATION ANALYSIS OF THE EFFECT OF PROSTAGLANDIN E1 ON ULCER HEALING (N = 60)

Model/path	Estimate (β or OR)	95% CI	*P* value	Interpretation
Outcome: Ulcer healing (Yes/No) | Mediator: ΔABI | Exposure: PGE1 (Yes vs No)				
Path c: PGE1 → ulcer healing (total association)	OR = 3.80	1.85-7.82	< .001*	Overall association of PGE1 use with healing (exploratory)
Path a: PGE1 → ΔABI	β = 0.18	0.09-0.27	.001*	PGE1 use associated with greater ABI gain
Path b: ΔABI → ulcer healing (adjusted for PGE1)	OR = 2.10	1.25-3.53	.005*	Greater ΔABI associated with higher healing odds
Path c': PGE1 → ulcer healing (direct association, adjusted for ΔABI)	OR = 2.69	1.20-6.03	.016*	Residual direct association after adjustment for ΔABI (exploratory)
Indirect association (a × b; mediated via ΔABI)	OR = 1.19	Bootstrap: 1.04-1.56	.046*	Portion of the association statistically consistent with a pathway via ΔABI (~31% of the total association; exploratory)
Mediation via ΔToe pressure (secondary analysis)				
PGE1 → ΔToe pressure (path a)	β = 9.4 mmHg	5.1-13.7	< .001*	PGE1 use associated with higher toe-pressure gain
ΔToe pressure → ulcer healing (path b)	OR = 1.82	1.10-3.01	.021*	Higher toe-pressure gain associated with healing odds

Mediation analysis was performed using regression-based methods with 5000 bootstrap resamples. Linear regression was used for the mediators (ΔABI and ΔToe pressure), and logistic regression was used for the binary outcome (ulcer healing). Adjusted models included age, diabetes mellitus, baseline ABI, and lesion characteristics as covariates. Estimates describe associations in this cohort and are not treatment effects. Given the small sample, few ulcer-healing events, and nonrandomized allocation, these mediation estimates are exploratory only and should not be interpreted as causal effects, beneficial effects, or independent benefits of PGE1. Δ indicates change from baseline to 6 months. *P < .05 was considered statistically significant. Abbreviations: β, regression coefficient; PGE1, prostaglandin E1; OR, odds ratio; ABI, ankle-brachial index.

was also associated with greater ABI gain (β = 0.18) and higher toe pressure (β = 9.4 mm Hg). These estimates describe associations in this cohort and are not interpreted as treatment effects.

Subgroup comparison (**Table 5**) indicated better outcomes in the PGE1 group, with greater improvement in ABI (0.38 ± 0.09 vs 0.29 ± 0.11), higher toe pressure gain (26 vs 17 mm Hg), and greater pain reduction (−5.2 ± 1.1 vs −3.8 ± 1.3). More patients in the PGE1 group achieved ulcer healing (15 [88.2%] vs 10 [62.5%]), with shorter healing time (72 vs 102 days) and improved limb salvage (29 [96.7%] vs 24 [80.0%]), while fewer patients required major amputation (1 [3.3%] vs 6 [20.0%]). Vessel patency was higher in the PGE1 group (26 [86.7%] vs 21 [70.0%]), although this difference was not statistically significant.

In exploratory multivariable models, PGE1 use remained associated with greater ABI gain, greater pain reduction, and higher odds of ulcer healing and limb salvage after adjustment for the measured covariates (**Table 6**). These adjusted associations do not establish a treatment effect. After adjusting for propensity scores, PGE1 therapy remained significantly associated with improved hemodynamic and clinical outcomes, supporting the robustness of the findings (**Table 7**).

Discussion

The present study evaluated the relationship between hemodynamic improvement and functional outcomes following endovascular revascularization in patients with CLTI, while also examining the adjunctive role of PGE1. The findings demonstrated significant improvements in hemodynamic parameters, pain reduction, ulcer healing, and limb-related outcomes over a 6-month follow-up. Importantly, greater hemodynamic gains were consistently associated with superior clinical recovery, highlighting the relevance of objective hemodynamic metrics in predicting patient-centered results.

Although the association between hemodynamic improvement after revascularization and better clinical outcomes is not an entirely novel finding, the present study provides useful real-world observational data from a South Asian cohort. In particular, the concurrent evaluation of adjunctive intra-arterial PGE1 therapy, an area that remains incompletely addressed in current guidelines, adds a clinically relevant dimension. By demonstrating associations between greater hemodynamic gains, PGE1 use, and improved pain relief, ulcer healing, and limb salvage, this work generates hypotheses for future prospective studies and supports further investigation of microcirculatory-targeted adjuncts in CLTI management.

A key observation was the marked improvement in ABI and toe pressure following revascularization, which was accompanied by a substantial reduction in pain scores and favorable wound healing. This supports the fundamental principle that the restoration of macrovascular flow improves distal tissue perfusion, thereby alleviating ischemic symptoms. Similar improvements in ABI following endovascular therapy have been reported by Reed et al,[14] who demonstrated that hemodynamic recovery correlates

TABLE 5. SUBGROUP COMPARISON OF OUTCOMES BETWEEN PROSTAGLANDIN E1 AND NON-PROSTAGLANDIN E1 GROUPS (n = 60)

Outcome	PGE1 group (n = 30)	Non-PGE1 group (n = 30)	Test statistic	*P* value
Hemodynamic outcomes				
ΔABI (mean ± SD)	0.38 ± 0.09	0.29 ± 0.11	t = 3.62	.001*
ΔToe pressure (mm Hg), median (IQR)	26 (19-33)	17 (11-25)	U = 267.0	.003*
Pain and functional outcomes				
ΔVAS (mean ± SD)	−5.20 ± 1.10	−3.80 ± 1.30	t = 4.61	< .001*
Wound/ulcer outcomes (PGE1 n = 17 vs non-PGE1 n = 16 with ulcers)				
Ulcer healed, n (%)	15 (88.2)	10 (62.5)	χ^2 = 3.21	.042*
Time to healing (days), median (IQR)	72 (55-96)	102 (78-130)	U = 71.50	.018*
Limb outcomes (n = 30 per group)				
Limb salvage, n (%)	29 (96.7)	24 (80.0)	χ^2 = 4.04	.044*
Major amputation, n (%)	1 (3.3)	6 (20.0)	Fisher's exact	.044*
Vessel patency, n (%)	26 (86.7)	21 (70.0)	χ^2 = 2.61	.106

Data are presented as mean ± SD, median (IQR), or frequency (percentage) as appropriate. Independent samples t-test was used for normally distributed variables, and Mann–Whitney U test was used for non-normally distributed variables. Chi-square or Fisher's exact test was used for categorical variables. Δ indicates change from baseline; *P < .05 was considered statistically significant. Abbreviations: PGE1, prostaglandin E1; ABI, ankle-brachial index; VAS, visual analog scale.

with improved clinical outcomes in patients with CLTI. Reed et al[15] demonstrated that greater hemodynamic improvement following endovascular revascularization is associated with a shorter time to wound healing and reduced major adverse limb events. However, consistent with prior evidence, our findings suggest that hemodynamic improvement alone does not fully explain clinical recovery, indicating the influence of microvascular and tissue-level factors.

The correlation analysis further strengthened this relationship, showing that greater improvement in ABI and toe pressure was associated with faster ulcer healing, reduced pain, and improved limb salvage. These findings are in agreement with the concept that hemodynamic parameters serve as reliable surrogate markers for tissue perfusion and healing potential.[16] Previous studies have similarly demonstrated moderate correlations between ABI improvement and symptomatic relief, although variability exists owing to factors such as neuropathy, inflammation, and microcirculatory dysfunction.[5-7]

An important aspect of this study was the evaluation of adjunctive PGE1 therapy. Patients who received PGE1 were observed to have greater improvement in hemodynamic parameters, more pronounced pain reduction, and better wound healing outcomes than those who did not receive adjunctive therapy. These findings are consistent with the known pharmacological effects of PGE1, including vasodilation, inhibition of platelet aggregation, and enhancement of microcirculatory flow.[12] Experimental and clinical studies have shown that PGE1 improves capillary perfusion and tissue oxygenation, which are critical determinants of wound healing.[17-19]

Saha et al[18] reported significant improvements in pain and functional outcomes with PGE1 therapy in patients with CLTI, supporting its clinical utility. Several clinical studies have specifically evaluated PGE1 in patients with CTLI, reporting improvements in rest pain, ulcer healing, and limb salvage rates.[19-21] Although results across trials have been heterogeneous, these data support further investigation of PGE1 as an adjunctive therapy in selected patients with CLTI.

According to the Global Vascular Guidelines on CLTI, successful management of CLTI requires not only restoration of inline flow but also optimization of the microcirculation and comprehensive wound care.[22] Our observation that greater hemodynamic improvement was associated with better pain relief, ulcer healing, and limb salvage is consistent with this framework. The additional associations seen with adjunctive PGE1 further highlight the potential relevance of therapies targeting the microcirculation, an area that remains incompletely addressed in current guidelines and warrants further investigation.

The mediation analysis was performed as an exploratory, hypothesis-generating assessment of whether the observed association between PGE1 use and ulcer healing was statistically consistent with a pathway through ABI change. In this model, part of the association appeared to travel with greater ABI gain, while a residual direct association remained after adjustment for ABI change. These path estimates should not be read as evidence that PGE1 exerts beneficial effects or independent benefits, or as proof of a dual mechanism of action. With a small sample, few ulcer-healing events, and nonrandom treatment allocation, the mediation model is underpowered and vulnerable to residual confounding and overfitting. Prior PGE1 trials have also been heterogeneous. A small double-blind trial found no significant effect of intravenous PGE1 on rest pain or ulcer healing,[23] whereas a meta-analysis of randomized studies in Fontaine stages III and IV reported higher rates of ulcer healing or pain relief, and fewer amputations or deaths, than placebo.[24] Those studies evaluated PGE1 as primary medical therapy, not as an adjunct to tibial angioplasty, so they provide context only and do not establish a treatment effect in the present cohort.

Subgroup analysis showed more favorable outcomes in the PGE1 group across multiple outcomes, including ulcer healing, time to healing, and limb salvage. Although vessel patency was

TABLE 6. MULTIVARIABLE REGRESSION ANALYSIS OF PROSTAGLANDIN E1 EFFECT ON CLINICAL OUTCOMES

Outcome	Variable	Adjusted estimate (β/OR)	95% CI	*P* value
ΔABI	PGE1 therapy	β = 0.16	0.07-0.25	.001*
ΔVAS	PGE1 therapy	β = −1.25	−1.90 to −0.60	< .001*
Ulcer healing	PGE1 therapy	OR = 2.85	1.30-6.20	.008*
Limb salvage	PGE1 therapy	OR = 3.10	1.05-9.20	.041*

Models adjusted for age, diabetes mellitus, baseline ABI, and lesion characteristics. Δ indicates change from baseline; *P < .05 was considered statistically significant. Abbreviations: β, regression coefficient; OR, odds ratio; ABI, ankle-brachial index; PGE1, prostaglandin E1; VAS, visual analog scale.

TABLE 7. PROPENSITY SCORE-ADJUSTED ANALYSIS OF PROSTAGLANDIN E1 THERAPY

Outcome	Adjusted estimate (β/OR)	95% CI	*P* value
ΔABI	β = 0.14	0.05-0.23	.002*
Ulcer healing	OR = 2.60	1.20-5.65	.015*
Limb salvage	OR = 2.90	1.01-8.30	.047*

Δ indicates change from baseline; *P < .05 was considered statistically significant. Abbreviations: OR, odds ratio; β, regression coefficient; ABI, ankle-brachial index.

higher in the PGE1 group, the difference did not reach statistical significance, which may be attributed to the small sample size. Similar inconsistencies have been reported in previous studies, such as those by Nehler et al,[17] in which prostaglandin analogs did not significantly influence long-term patency despite improving clinical symptoms. These findings suggest that the primary benefit of PGE1 may lie in improving microcirculatory function rather than altering the patency of large vessels.

From a clinical perspective, the findings of this study have important implications. First, they reinforce the value of hemodynamic assessment, particularly ABI and toe pressure, as practical and objective tools for monitoring treatment response and predicting the outcomes. Second, they suggest a potential association between adjunctive pharmacological therapy targeting the microcirculation and improved outcomes, especially in patients with advanced disease or suboptimal perfusion after revascularization. This approach may be particularly relevant in diabetic populations, where microvascular dysfunction plays a major role in disease progression and healing delay.

However, this study has several limitations that must be considered. The retrospective design of this study introduces potential selection bias and limits the ability to establish causal relationships. The modest sample size (n = 60) and relatively small number of outcome events limit the statistical power and reliability of all conclusions, including the multivariable and propensity-score–adjusted analyses. The follow-up period of 6 months may not fully capture long-term outcomes, such as restenosis or sustained limb salvage. Additionally, variability in wound care practices and adjunctive medical therapy may have influenced the observed results. Formal Wound, Ischemia, and foot Infection staging was not systematically recorded during the study period, as the classification was only introduced in 2014 and had not yet been widely adopted in routine practice at our center.[25] This limits precise baseline risk stratification according to current standards.

ABI measurements were obtained with handheld Doppler devices, which are operator-dependent and may introduce measurement variability compared with automated systems. The inclusion of adjunctive PGE1 therapy as an observed treatment variable adds complexity to the interpretation of the findings. Because allocation was nonrandomized and at the discretion of the treating physician, residual selection bias and confounding may persist despite statistical adjustment. Although multivariable regression and propensity-score adjustment were performed, the modest sample size (n = 60) and relatively small number of outcome events raise concerns regarding model stability and possible overfitting. In particular, statements about mediation should be read only as exploratory associations; the analysis cannot support claims of beneficial effects or independent benefits of PGE1. The statistical analyses should therefore be interpreted with caution.

Conclusions

Endovascular revascularization in CLTI was associated with significant improvements in hemodynamic parameters, pain relief, and wound healing over 6 months. Hemodynamic improvement, reflected by increases in ABI and toe pressure, was strongly associated with better functional outcomes, including faster ulcer healing and improved limb salvage. Adjunctive PGE1 therapy was associated with greater hemodynamic change, ulcer healing, and limb salvage. Mediation analysis suggested that part of the healing association was statistically consistent with ABI change, with a residual direct association. These are exploratory associations only and are not evidence of beneficial effects or independent benefits of PGE1. Given the small sample and the retrospective, nonrandomized design, causality cannot be established. Larger prospective studies with longer follow-up are warranted before these observations can inform treatment protocols.

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The author reports no financial relationships or conflicts of interest regarding the content herein.

Manuscript accepted October 7, 2026.

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