Chronic Total Occlusions: Association Between Characteristics and Mid-Term Outcomes in Critical Limb Ischemia

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Abstract

Background. Despite medical advancements, peripheral artery disease (PAD) and critical limb ischemia (CLI) continue to increase globally. Treatment for PAD/CLI varies widely and patients with chronic total occlusions (CTO) may be more challenging to treat, requiring specialized crossing techniques and modalities. The objective of this study was to determine the relationship between patients diagnosed with PAD/CLI, with CTOs, and subsequent long-term outcomes. **Methods.** Retrospective analysis on prospectively captured data was completed for subjects undergoing an endovascular revascularization for symptomatic PAD/CLI with a CTO. Vascular access and treatment modality were chosen by the treating physician. CTO characteristics and outcomes were collected and categorized by a novel PRIME scoring system rating length, complexity, and lesion location. Predictors for CTO location and freedom from target lesion revascularization, amputation, and mortality were analyzed. **Results.** Of 411 subjects/procedures, the majority were PRIME lesion type 2 (40.4%) or 4 (30.1%). The least common was PRIME 6 (1.7%). Statistically significant differences were found among groups with above-the-knee (ATK) lesions, multilevel lesions, and below-the-knee (BTK) lesions with respect to risk factors, symptomology, and outcomes. Freedom from 1-year mortality and amputation were lowest for the BTK subject group. Subjects with multilevel lesions were found to have a greater need for target lesion revascularization within 1-year. **Conclusions.** Within the realm of PAD, CTO arterial lesions represent a complex subset. Characteristics of CTOs such as lesion location and distribution appear to affect long term outcomes. Evaluating individual patient presentation could aid in the determination of treatment strategies and long-term disease management.

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Peripheral artery disease (PAD) is a complex disease that continues to escalate in prevalence globally. Despite medical advancement, the number of PAD cases worldwide increased by 25% from 2000-2010 with a global burden of 202 million cases in 2010. The number of cases are most likely underestimated for a variety of reasons.[1] The disease process represents a broad spectrum of manifestations that range from asymptomatic disease to extensive tissue loss and gangrene with disease severity not necessarily mirroring the symptoms at presentation.[2-4] In some cases, the patient's symptoms accurately portray ischemic progression while, for others, the disease process progresses silently until the patients develop severe ulcers or gangrene.[4] Critical limb ischemia (CLI) represents the most advanced form of PAD and 29% of CLI diagnoses result in death or major amputation within the first year.[5] Parallel to the varied manifestations or symptoms, PAD has diverse anatomical and pathological patterns. The multilevel disease process requires a wide range of treatment strategies focused upon the patient's unique lesion characteristics.[6,7]

Chronic total occlusions (CTO) represent a challenging subset of peripheral arterial lesions requiring endovascular intervention.[8,9] Distinctive from coronary artery disease, the dense, collagenous lesions are often long and characterized by organized occlusive thrombi that result from cyclic silent episodic ruptures with subsequent healing. This process is compounded with further calcific

deposit involving the vessels and its layers.[6,10] Positive and negative remodeling of vessels impact the complexity of revascularization. CTOs are primarily located in the femoropopliteal segment for patients who suffer from claudication (Rutherford Classification [RC] 2 and 3). This is in contrast to CLI patients where the disease tends to be more distal in the popliteal and tibial vessels.[11] The location and extent of arterial occlusions directly impacts the crossing techniques and treatment modalities required for successful intervention.[6,10] Due to the complex aspects of PAD, ongoing investigation of the relationship between lesion characteristics and patient's baseline presentation with morbidity and mortality outcomes is essential to improve outcomes in this complex patient population. This manuscript examines the relation between PAD/CLI patients with CTOs and associated long-term outcomes.

Methods

Subjects. This retrospective analysis of prospectively collected data was assembled as part of the Peripheral RegIstry of Endovascular Clinical OutcoMEs (PRIME Registry), a multi-center registry of PAD and CLI subjects who underwent lower extremity endovascular revascularization in five centers in the United States between January 2013 and February 2018. Institutional Review Board approval was obtained at each institution and subject consent was obtained prior to any procedures or data collection. Eligible subjects were adults ≥18 years with symptomatic PAD (Rutherford class 2-3) and CLI (Rutherford class 4-6) undergoing endovascular intervention for a CTO.[10] Although the PRIME participants may have required multiple interventions due to bilateral disease, to ease analysis, only the index procedure for enrollment on the PRIME Registry was used for this study.

Procedure. Endovascular revascularization was attempted on all study subjects. Vascular access and revascularization methods were determined by the treating physician and included one or a combination of the following: atherectomy, percutaneous transluminal angioplasty (PTA), drug-coated balloon angioplasty (DCB), bare-metal stent (BMS) or drug-eluting stent (DES) placement. Patients may have had more than one CTO treated during the endovascular procedure. If more than one CTO was treated, the location of the patient's target lesions were based on the location of both lesions. For example, if both CTO lesions were above-the-knee (ATK), then the patient's disease was classified as ATK for analysis, and subsequently, if both target lesions were below-the-knee (BTK) the disease would be analyzed as BTK. If one of the subject's target CTOs was ATK and one was below the knee (BTK), then the subject/procedure would be classified as multilevel.

Study endpoints. Demographics and baseline symptomology were collected to determine predictors for CTO location. Calcification and lesion length were established by operator visual estimate. Clinical outcomes of target lesion revascularization, amputation, and death were also collected to determine freedom from target lesion revascularization, major and minor amputation, and mortality for participants with CTOs. A target lesion revascularization was a subsequent vascular intervention of a subject's index procedure CTO. Major amputation consisted of above the knee amputation or below the knee amputation of the target limb treated in the index procedure. Minor amputation was documented if a subject had a recorded removal of the foot or toes (below the ankle) on the target limb.

Data analysis. Patient characteristics and lesion characteristics were reported as mean ± standard deviation for normally distributed continuous variables; median, interquartile range, minimum, and maximum for non-normally distributed continuous variables; and frequency and count for categorical variables. Data were reported on a per patient, per procedure, or per CTO basis. Comparisons of patient and lesion characteristics by CTO location were performed with analysis of variance, Kruskal-Wallis test, or Fisher's exact test. Comparisons of clinical outcomes by CTO location were performed using Kaplan-Meier methods. The association of baseline characteristics with clinical outcomes was evaluated using a Cox proportional hazards model. Variables that entered the model at $P<.10$ were entered in a multivariable model where only variables with a P-value below .05 remained in the final model. All analyses were performed using Stata, version 16.0.

PRIME category. CTOs with corresponding arterial disease were categorized by the following PRIME lesion locations. The length and/or complexity of CTOs increase with higher PRIME category:

(A) PRIME 1: originates and reconstitutes in iliac arteries.
(B) PRIME 2: originates in superficial femoral artery and reconstitutes in superficial femoral or popliteal arteries.
(C) PRIME 3: originates in superficial femoral or popliteal arteries and reconstitutes in tibial arteries.
(D) PRIME 4: originates and reconstitutes in tibial arteries.
(E) PRIME 5: originates in tibial arteries and reconstitutes in pedal arteries.
(F) PRIME 6: extends from superficial femoral artery to the pedal circulation.

For analysis, the PRIME locations were further categorized into 3 different cohorts:

(1) Above-the-knee (ATK): PRIME 1 and PRIME 2.
(2) Below-the-knee (BTK): PRIME 4 and PRIME 5.
(3) Multilevel: PRIME 3 and PRIME 6.

Results

Patient characteristics. Mean age of patients was 70 years with 63% male. The patients were predominantly white (93%). As shown in **Table 1**, the most common comorbidities were hypertension

TABLE 1. Patient characteristics.

Demographics	N	Value
Age (years)	411	69.9 ± 11.4
Male sex	411	259 (63.0%)
Body mass index (kg/m^2)	408	29.8 ± 8.4
Race	406	
White		377 (92.9%)
Black		27 (6.7%)
Other		2 (0.5%)
Medical history	**N**	**Value**
Peripheral artery disease	411	373 (90.8%)
Hypertension	411	360 (87.6%)
Dyslipidemia	411	352 (85.6%)
Smoking history	411	308 (74.9%)
Diabetes mellitus	411	238 (57.9%)
Coronary artery disease	411	227 (55.2%)
Myocardial infarction	411	89 (21.7%)
Congestive heart failure	410	81 (19.8%)
Atrial fibrillation	410	67 (16.3%)
Chronic obstructive pulmonary disease	411	67 (16.3%)
Cerebrovascular disease	409	61 (14.9%)
Creatinine	408	1.1 (0.9-1.4) [0.3, 9.2]
GFR	394	60 (46-78) [6, 318]
<60		187 (47.5%)
<30		37 (9.4%)
Dialysis-dependent renal failure	411	22 (5.4%)
Rutherford classification	409	
2		1 (0.2%)
3		109 (26.7%)
4		110 (26.9%)
5		167 (40.8%)
6		22 (5.4%)

Data reported as number (percentage), mean ± standard deviation, or median (interquartile range) [min, max]. N = number of available data for analysis of an endpoint and value = n (%).

TABLE 2. Lesion characteristics.

Characteristic	N	Value
Chronic total occlusion	485	485 (100%)
Chronic total occlusion location	411	
Above the knee		141 (34.3%)
Below the knee		151 (36.7%)
Multilevel		119 (29.0%)
PRIME lesion type	485	
PRIME 1		38 (7.8%)
PRIME 2		196 (40.4%)
PRIME 3		23 (4.7%)
PRIME 4		146 (30.1%)
PRIME 5		67 (13.8%)
PRIME 6		8 (1.7%)
Other - Profunda		7 (1.4%)
Calcification[a]	457	393 (86.0%)
In-stent occlusion	485	47 (9.7%)
Thrombus[b]	483	36 (7.4%)
Peak diameter (mm)[c]	438	4.7 ± 1.6
Lesion length (mm)	462	200 (100-300) [5, 750]

Data reported as number (percentage), mean ± standard deviation, or median (interquartile range) [min, max]. N = number of available data for analysis of an endpoint and value = n (%).
[a] Calcification defined as focal or diffuse calcium build-up within the target lesion by physician visual documentation.
[b] Thrombus defined as any clot, fresh or chronic located in the target vessel prior to treatment.
[c] Peak diameter defined as the largest diameter of the target lesion, per physician visual estimate.

(88%), dyslipidemia (86%), diabetes (58%), coronary artery disease (55%), and renal disease (57%). The majority of patients (73%) had CLI (RC 4-5).

Lesion characteristics. As demonstrated in **Table 2**, 485 CTO lesions were treated in 411 procedures. By operator visual estimate, most CTOs were calcified (86%) with median lesion length of 200 mm. CTO disease was categorized by ATK, BTK, and multilevel locations (34%, 37% and 29%, respectively) as well as PRIME arterial locations. Within the PRIME lesion cohorts, the majority were classified as PRIME 2 or PRIME 4 (40% and 30%, respectively) with PRIME 6 (2%) representing the least common yet most extensive disease.

TABLE 3. Patient and lesion characteristics by chronic total occlusion location.

Characteristic	ATK PRIME 1 & 2	Multilevel PRIME 3 & 6	BTK PRIME 4 & 5	*P*-Value
Age, years	68 ± 10	71 ± 12	71 ± 11	.02
Male sex	61%	61%	67%	.47
Hypertension	92%	83%	87%	.13
Dyslipidemia	87%	85%	85%	.80
Smoking history	92%	80%	56%	<.001
Diabetes mellitus	50%	50%	72%	<.001
Coronary artery disease	59%	50%	56%	.40
Myocardial infarction	27%	21%	17%	.13
Congestive heart failure	18%	19%	23%	.58
Atrial fibrillation	9%	17%	23%	.008
Chronic obstructive pulmonary disease	22%	15%	12%	.06
Cerebrovascular disease	11%	19%	15%	.32
GFR <60	37%	45%	59%	<.001
GFR <30	3%	9%	16%	<.001
Dialysis-dependent renal failure	3%	3%	9%	.03
Rutherford				<.001
2	1%	0%	0%	
3	50%	25%	6%	
4	29%	30%	23%	
5	17%	39%	65%	
6	4%	6%	7%	
Calcification	93%	88%	95%	.11
Lesion length (mm)	238 ± 146	224 ± 136	231 ± 135	.71

Data reported as percentage or mean ± standard deviation.
ATK = above the knee; BTK = below the knee; GFR = glomerular filtration rate.

Characteristics and outcomes by CTO location. Baseline characteristics. Patient and lesion characteristics and treatment outcomes were analyzed and compared by ATK, BTK, and multilevel CTO locations (**Table 3** and **Table 4**). History of smoking, diabetes, and renal insufficiency (demonstrated by altered glomerular filtration rates) were statistically significant between the cohorts. A higher percentage of patients with CTO locations ATK reported a history of smoking versus those with multilevel or BTK locations (92%, 80%, and 56%, respectively; *P*<.001). 72% of patients with BTK occlusions presented with history of diabetes versus 50% with ATK and multilevel locations. BTK patients also had a significantly higher percentage of renal insufficiency (75%) versus those with ATK (40%) and multilevel disease (54%). For claudicants (RC 3), CTO locations were more commonly located ATK while a higher percentage of occlusions were situated BTK for RC 5 patients. The CTO locations for CLI patients with rest pain (RC 4) were more equally dispersed with 29% ATK, 23% BTK and 30% multilevel. Differences of lesion length and calcification were not significant between the 3 cohorts.

One-year outcomes. Significant differences were identified when evaluating freedom from 1-year mortality and major amputation with superior outcomes noted for patients with ATK occlusions. Freedom from 1-year mortality was 97% for ATK, 86% for multilevel, and 84% for BTK (*P*<.01) with freedom from 1-year major amputation rates of 99%, 96%, and 90%, respectively (*P*<.01). A greater number of patients with multilevel occlusions required target lesion revascularizations within the first year (32%) compared to those with occlusions located above or below-the-knee (23% for both cohorts) (**Table 4**).

Predictors for clinical outcomes. Further analyses were performed to evaluate the direct association between patient and lesion characteristics with 1-year clinical outcomes (**Table 5**). Within univariate models, significant risk ratios were noted in comparison of mortality rates for patients who presented with PAD (RC 2 or 3) versus CLI (RC 4-6). Correspondingly, statistically significant differences in 1-year mortality risk ratios were also identified when comparing ATK versus multilevel or BTK cohorts (*P*<.01). Need for dialysis was found to have a clinically significant risk ratio (*P*<.001) for major amputation but no predictors were noted as clinically significant risks for target lesion revascularization by univariate or multivariate model.

TABLE 4. Clinical outcomes by chronic total occlusion location.

Characteristic	ATK PRIME 1 & 2	Multilevel PRIME 3 & 6	BTK PRIME 4 & 5	*P*-Value
Freedom from 1-year mortality	97.1%	86.2%	83.8%	<.01
Freedom from 1-year major amputation	98.5%	95.6%	89.6%	<.01
Major amputation-free survival through 1 year	95.6%	82.0%	76.6%	<.001
Freedom from 1-year target-lesion revascularization	77.0%	68.0%	76.8%	.26

Data reported as percentage or mean ± standard deviation. ATK = above the knee; BTK = below the knee.

TABLE 5. Association of baseline characteristics with clinical outcomes at 1 year of follow-up.

Characteristic	Mortality			Major Amputation			Target-Lesion Revascularization		
	Risk Ratio	95% CI	*P*-Value	Risk Ratio	95% CI	*P*-Value	Risk Ratio	95% CI	*P*-Value
Univariate model									
Age, per 10-year increase	1.44	1.09-1.91	.01	1.07	0.74-1.56	.70	1.07	0.90-1.27	.45
CTO location, BTK/multilevel vs ATK	5.43	1.94-15.2	.01	5.49	1.28-23.5	.02	1.24	0.81-1.89	.32
Sex, male vs.female	1.28	0.68-2.42	.44	2.05	0.76-5.55	.16	1.13	0.75-1.70	.55
Smoking history, never vs any	2.19	1.20-4.00	.01	1.48	0.60-3.63	.39	1.28	0.83-1.98	.26
Diabetes mellitus, yes vs no	1.77	0.93-3.38	.08	3.37	1.14-9.96	.03	1.36	0.91-2.03	.14
Dialysis, yes vs no	3.12	1.32-7.37	<.01	9.96	4.05-24.5	<.001	1.87	0.91-3.86	.09
Disease severity, CLI vs PAD	8.04	1.95-33.2	<.01	8.29	1.12-61.6	.04	1.11	0.71-1.73	.64
Calcification, any vs none	1.78	0.43-7.37	.43	0.84	0.20-3.62	.82	0.66	0.35-1.23	.19
Lesion length, per 100 mm decrease	1.01	0.81-1.26	.96	1.10	0.80-1.52	.55	0.99	0.86-1.14	.89
Multivariate model									
CTO location, BTK/multilevel vs ATK	3.48	1.22-9.94	.02	4.80	1.12-20.6	.03	—	—	—
Disease severity, CLI vs PAD	5.20	1.22-22.1	.03	—	—	—	—	—	—
Dialysis, yes vs no	—	—	—	8.78	3.55-21.7	<.001	—	—	—

Discussion

CTOs are a challenging subset of lesions which are commonly the result of severe, concentric intimal thickening or occlusive thrombi organized from cyclic episodic ruptures with subsequent healing.[6,12] Arterial calcification is increasingly recognized as a primary constituent of the complex pathological PAD features with medial and intimal calcification coexisting in varying frequencies.[13] Infrapopliteal disease has higher rates of medial calcification. There is distal progression of the disease as you evaluate the tibial vessels to the plantar circulation. The deposition of arterial calcium increases with decreased burden of fibro-fatty plaque.[6,14] Due to the heterogenous pathophysiology within the peripheral arterial bed, lesion characteristics are a key factor that must be examined in the determination of PAD and CLI treatment strategies. Location, length, degree of calcification, and percent stenosis must all be considered as treatment success cannot occur with a one size fits all modality or algorithm.[7] In the 411 patients studied, the percentage of CTOs and corresponding disease located ATK, BTK, or multi-level were comparable in number (34%, 37%, 29%, respectively), yet the study found that CTO location was associated with significant differences in patient outcomes through one year. Patients with CTOs located BTK were found to have the highest mortality and amputation in comparison to those ATK or multilevel. The pathophysiologic process of ATK and BTK arterial beds vary drastically, and the treatment modalities utilized must address the unique components of disease presentation.

PAD patients commonly have a complicated medical presentation with the known risk factors of hypertension, diabetes, smoking history, cardiovascular disease, hypercholesterolemia, and renal disease.[1,15] In comparison of patient's medical history and CTO location, it was found that patients with a history of smoking were more likely to have ATK occlusions while history of diabetes and renal disease, including end-stage renal disease (ESRD), were more common in patients with BTK occlusive disease process. The impact of these comorbidities extends beyond the complexity of lifelong patient management as each have been found to directly impact degree of medial calcification in peripheral arteries. Diabetes and ESRD have been associated with an increased severity of medial calcification while histopathologic analysis revealed that smoking was associated with less prevalence in BTK disease.[12] The patients' presenting RCs also had a significant correlation with disease location as patients with claudication symptoms (RC 3) were more likely to have ATK disease while patients with non-healing, ischemic wounds had higher likelihood of BTK disease. Interestingly, the disease location of patients who presented with RC 4 symptoms was similar between the ATK, BTK, and multilevel cohorts (29%, 30%, 23%, respectively). This may be explained by the fact that claudication (RC 1-3) and wounds (RC 5&6) are well defined clinical presentations; however, RC 4 pain may be more difficult

to define due to other reasons such as neuropathy that may affect the even lesion distribution. If all RC 4 patients would have real ischemic rest pain, one could infer that the lesion distribution should be more like the RC 5&6 cohort. The majority of clinical trials direct investigational study for RC 3 patients to ATK disease while treatment for CLI patients is focused upon targeted lesions BTK. Within the PRIME population evaluated, all RC 3-6 categories had a certain percentage of patients within the above-the-knee, below-the-knee, and multilevel cohorts. Due to this disbursement, the focused scope of clinical investigations may limit the ability to apply the findings to the generalized and diverse PAD and CLI populations.

Evaluation of 1-year outcomes revealed that patients who presented with ATK occlusions had significantly lower rates of mortality and amputation. Major amputation-free survival through 1-year was 96% for the ATK cohort, 82% for multilevel and 77% for BTK ($P<.001$). While one-fourth of patients with RC 3 presented with multilevel occlusive disease and 6% with BTK occlusions, the majority of patients within these cohorts had CLI. A recent analysis of 72,199 Medicare beneficiaries with CLI revealed grave long-term outcomes with 29% of patients experiencing death or major amputation within the first year, and, over 4 years, mortality rates increased to greater than 50%.[5] The discouraging outcomes of this analysis were unfortunately supported by an observational study of long-term outcomes following various revascularization treatment strategies for CLI. When evaluating 36,860 CLI patients, all-cause mortality over a 4-year period was 49% for patients treated with atherectomy, 51% with surgical bypass, 54% for stent placement and 55% with percutaneous transluminal angioplasty.[7] Neither of these evaluations accounted for lesion location or characteristics within these findings and the inclusion of some RC 3 patients within the PRIME multilevel and BTK cohorts may explain the superior amputation-free survival outcomes at 1-year. Notwithstanding, the long-term outcomes for patients presenting with occlusive multilevel or BTK disease are dismal. Risk ratio analysis revealed that CTO location was associated with mortality rates with multilevel and BTK occlusions significantly predicting greater risk.

Within the PRIME CTO analysis, the majority of patients evaluated presented with CLI. The goals of CLI management include wound healing and limb preservation, improvement in quality of life, and prolonged survival.[16] One-year results of the Liberty 360 study supported the benefit of endovascular revascularization with improvement in RC and quality of life noted across all cohorts, including the most complex and difficult to treat patients with RC 6 presentation.[3] The value of decreasing patient's pain attributed to ischemia and chronic wounds, increasing their physical and social functioning, and diminishing the risk of amputation and mortality, which then diminishes overall anxiety and depression, is a pertinent treatment goal that should not be undervalued in this chronic disease.[17,18] Within clinical trials, ongoing patency and avoidance of reinterventions is a primary focus yet the application of this endpoint is controversial due to the vast spectrum of complexity and severity that exists within CLI disease.[19] The determination of optimal treatment algorithms and guidelines as well as indicators for long-term success is complicated and multilayered as CLI patients cannot be stratified solely by one component of their presentation. Medical history and comorbidities, RC presentation, and unique lesion characteristics must all be comprehensively evaluated as each uniquely impacts ideal treatment strategies and outcomes. The development of risk stratification schemes that encompass the multifaceted components of CLI presentation has been suggested to better define and direct long-term therapy.[19,20] Within the PRIME CTO analysis, patients with multilevel occlusions had superior freedom from mortality (86%) and amputation (96%) at one-year compared to those with BTK occlusions (84%, 90%, respectively). However, more target lesion revascularizations (TLR) were required within the multilevel cohort versus BTK cohort (32% vs 23%). While some of the rates compared are not drastically different, these data may suggest that TLRs contribute to diminished long-term mortality and amputation rates. In determination of individualized CLI treatment goals, increased frequency of TLRs may be required to achieve a more global measure of amputation-free survival with improved quality of life[19] and, therefore, TLRs may be an expected component of long-term treatment guidelines rather than a measure of treatment failure. As CTO location and RC were associated with mortality risk, it is imperative that practitioners do not take a wait and see approach when presented with BTK or multilevel CLI occlusive disease.

Study limitations. This is a clinical registry with the inherent limitations of a non-randomized, observational design. In addition, the lesion characteristic findings were not core lab adjudicated. Certain CTO cohorts had smaller numbers which may limit the overall significance of the findings.

Conclusions

PAD is a multifaceted disease process with a broad spectrum of manifestations and pathological patterns that influence clinical outcomes. CTOs represent a complex subset of arterial lesions and the evaluation of CTO characteristics revealed that location and distribution impact long-term outcomes. Each patient's unique presentation should be comprehensively evaluated in the determination of treatment strategies and long-term disease management. CLI patients with multilevel or BTK occlusive disease were associated with increased mortality risk. Whether early revascularization may impact short- and long-term outcomes will require further study.

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