Outcomes Among Patients With Chronic Critical Limb Ischemia With No Revascularization Option: Systematic Review and Meta-Analysis

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Abstract

Objectives. The natural history of patients with no-option Rutherford category 5/6 critical limb ischemia (CLI) is poorly characterized. To evaluate clinical outcomes in patients with Rutherford category 5/6 CLI who are not candidates for revascularization (no option) a meta-analysis was performed. **Methods.** Two prespecified literature searches were conducted via Ovid utilizing the following databases: MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews (CDSR). We selected studies reporting amputation-free survival (AFS) in patients with non-revascularizable Rutherford category 5/6 CLI at a minimum follow-up of 6 months. Because studies included patients with Rutherford categories 4, 5, and 6, the second search was conducted to identify hazard ratios for AFS or its components between patients with more severe (Rutherford category 5/6), compared with less severe (Rutherford category ≤4) disease, to inform appropriate risk adjustment. **Results.** We identified 32 studies meeting the selection criteria reporting AFS rates at 6 and/or 12 months. AFS rates improved in studies with enrollment ending after 2003 vs prior to 2003. In studies with enrollment ending after 2003, the unadjusted meta-analytic estimates of AFS rates at 6 and 12 months were 58.6% and 50.3%, respectively. The risk-adjusted meta-analytic estimates of AFS rates were 42.0% (95% confidence interval, 32.8-51.2) at 6 months and 33.3% (95% confidence interval, 21.1-45.5) at 12 months in no-option Rutherford category 5 or 6 CLI patients. **Conclusions.** Approximately 2 out of every 3 patients with advanced CLI who are not candidates for current revascularization approaches will die or require major amputation within 1 year.

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Globally, over 200 million people were reported to be living with peripheral arterial disease (PAD) in 2010, an increase of 13% over the previous decade in high-income countries and nearly 30% in low- and middle-income countries.[1] Approximately 10% of patients with advanced PAD have critical limb ischemia (CLI), defined as intractable foot pain at rest and/or tissue loss.[2] Healthcare costs associated with CLI in the United States exceeded $579 million in 2001 and increased to $870 million in 2007.[3]

Revascularization options for CLI patients include endovascular, surgical, or hybrid (both) techniques.[4] However, because of advanced diffuse disease, severe comorbidities, or anatomic limitations, it has been determined that 5%-20% of CLI patients are not candidates for conventional surgical or endovascular revascularization ("no-option" patients).[5-7] Little is known about the outcomes of patients with advanced (Rutherford category [RC] 5 or 6[8] or Fontaine stage IV[9]) CLI not suitable for revascularization with currently available surgical or endovascular approaches because the outcomes of this cohort are rarely reported separately from patients with less severe disease. To address this gap in knowledge, we performed a systematic review and meta-analysis to estimate contemporary rates of amputation-free survival (AFS) in patients with severe RC 5/6 CLI who are not eligible for surgical or endovascular revascularization.

Methods

This systematic review and meta-analysis was performed in accordance with PRISMA guidelines.[10]

TABLE 1. Trends in amputation-free survival rates by time of enrollment.

	Studies (n)	Events (n)	Total (n)	Weighted Average	*P*-Value
6-Month Amputation-Free Survival (Pre and Post 2003)					
Before 2003	8	217	449	48.3%	
After 2003	20	678	992	68.3%	
	Total	895	1441	62.1%	<.001
12-Month Amputation-Free Survival (Pre and Post 2003)					
Before 2003	6	219	463	47.3%	
After 2003	18	515.5	901	57.2%	
	Total	734.5	1364	53.8%	<.001
6-Month Amputation-Free Survival (2003-2010 vs 2010 and Later)					
Before 2010	7	399	580	68.8%	
After 2010	13	279	412	67.7%	
	Total	678	992	68.3%	.72
12-Month Amputation-Free Survival (2003-2010 vs 2010 and Later)					
Before 2010	7	323	545	59.3%	
After 2010	10	175	317	55.2%	
	Total	498	862	57.8%	.24

TABLE 2. Publications reporting unadjusted hazard ratio for Rutherford category 5/6 vs Rutherford category 4.

Study	Patients (n)	Patient Risk Profile	Variable	Event	Unadjusted Hazard Ratio	95% CI	Rutherford Category 4	Rutherford Category 5	Rutherford Category 6
Chung et al. 2013[29]	98	RC 4/5/6	RC 5/6 vs RC 4	AFS	1.56	1.01-2.41	40 (40.8%)	27 (27.5%)	31 (31.6%)
Soga et al. 2014[30]	995	RC 4/5/6	RC 5 vs RC 4	death	2.3	1.6-3.3	245 (25%)	505 (51%)	245 (25%)
Spreen et al. 2016[31]	281	RC 4/5/6	RC 5/6 vs RC 4	major amputation	2.03	1.28-3.21	NR	NR	NR

AFS = amputation-free survival; CI = confidence interval; NR = not reported; RC = Rutherford category.

Literature search. A prespecified literature search protocol was developed to identify data on clinical outcomes (at 6 months or later) of patients with non-revascularizable lower-extremity CLI. An exploratory search determined that nearly all such studies also included RC 4 patients; therefore, a second search was performed to quantify the relative hazard of CLI patients classified as high-risk (RC 5 or 6) in comparison with low-risk (RC 4) patients for the outcomes of interest. Both literature searches were conducted in February 2020 using Ovid (Wolters Kluwers) to search MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews from inception to the date of the search. Abridged search terms and strategies are reported in **Supplemental Table S1** and **Supplemental Table S2.**

Study selection. We selected randomized controlled trials, controlled trials without randomization, well-designed cohort or case-control studies, longitudinal series, and case series. Studies reporting outcomes in patients with non-revascularizable (according to each study's definition) lower-extremity CLI and RC 4, 5, or 6 or any symptomatic/ischemic equivalent were included (as described in **Supplemental Table S3**). Medical management, pain management, and wound care in accordance with non-experimental standard of care were permitted. The primary outcome of interest was *amputation-free survival (AFS)*, defined as freedom from the composite of all-cause mortality and major (above-the-ankle) amputation, reported at a minimum follow-up of 6 months.

For the supplemental search to establish an adjustment factor for RC 4 vs RC 5/6 disease, we selected studies of RC 4, 5, or 6 patients that reported hazard ratios (HRs) for outcomes (AFS, all-cause mortality, or major amputation) between high-risk (RC 5/6) and lower-risk (RC 4) patients. Because no studies of

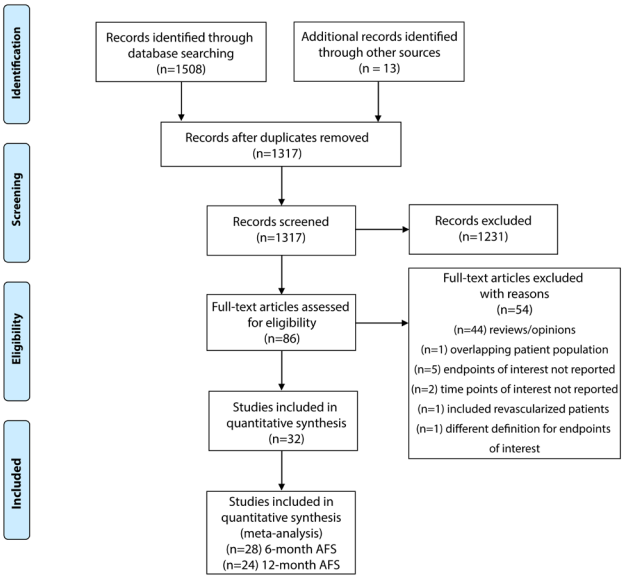

FIGURE 1. PRISMA flow diagram of systematic literature search for the meta-analysis. AFS = amputation-free survival.

no-option patients meeting these criteria were identified, the selection criteria for the supplemental search were expanded to allow studies reporting HRs between the groups of interest regardless of revascularization status. The results of the supplemental search were used only to establish the adjustment factor.

Two reviewers (MIG and DT) independently screened titles and abstracts; any discrepancies were resolved by consensus or by discussion with a third author (CP). Full-text articles were obtained for those that met criteria in the initial screen of abstracts and titles then further assessed for eligibility. The bibliographies of relevant articles and reviews were examined to identify additional publications for selection.

Data extraction and risk of bias assessment. Two investigators (MIG and DT) independently extracted data from the selected articles in duplicate. Any disagreements were resolved by consensus or with a third author (CP). We collected the number of patients, the number of limbs involved (when reported), the number of centers involved in the study, dates of enrollment, qualifying CLI criteria (RC, Fontaine stage, or symptomatic equivalent [ischemic rest pain, tissue loss, ulcer, gangrene, ankle pressure <70 mm Hg, toe pressure <50 mm Hg, flat pulse volume recording, or transcutaneous oxygen pressure <40 mm Hg]), baseline patient demographics, proportion of patients with each severity class/stage or symptomatic equivalent, history of vascular interventions, wound characteristics, and outcomes at 6 and 12 months (mortality, amputation, AFS, wound healing).

Risk of bias of individual studies was assessed with the Cochrane Collaboration's tool.[11] Studies were assessed on the basis of sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other sources of bias. Blinding and randomization were not performed in all studies; however, assessment of AFS was not likely to be influenced by these factors.

Data synthesis and statistical analysis. Data tables for all included studies were compiled and included number of subjects, event-free survivors, AFS rate, included RCs, proportion of patients with RC 5/6 (or symptomatic equivalent) disease, and enrollment end dates. If the enrollment end date was not reported for a study, it was imputed based on the date of manuscript submission or publication (first available). For studies that did not report the proportion of patients in each RC, the proportion of high-risk (RC 5/6) patients was imputed based on the average of all studies that reported this proportion.

As an initial analysis, overall AFS rates at 6 and 12 months were calculated by taking the meta-analytic average using inverse variance weighting and a random effects approach to account for the variability in the estimates and the potential heterogeneity of the studies. To determine whether there were significant changes in AFS event rates over time (eg, due to improved medical management) that may affect the generalizability of the study results to current clinical practice, an analysis of AFS by time of enrollment was performed. A Chi-square test was used to compare weighted averages for significant changes in AFS rates over different enrollment periods; a statistically significant difference in AFS rates by period of enrollment was used to establish an estimate of the period during which event rates could be considered "contemporary."

Finally, because most studies reporting AFS in no-option CLI patients included lower-risk subjects (RC 4), an adjustment factor was developed to better fit available historical data to the population of interest. HRs for outcomes (AFS, all-cause mortality, or major amputation) between high-risk (RC 5/6) and lower-risk (RC 4) patients were extracted from studies identified in the second literature search. An adjustment factor for AFS rates was calculated from the reported HRs by log transforming the HR, calculating the weighted average of the log HR, and inverting to the arithmetic scale. The adjustment factor was then applied to the observed AFS rates in the applicable studies of no-option CLI patients according to the proportion of RC 5/6 and RC ≤4 patients in each study to arrive at an adjusted AFS rate for each study according to the following formula:

Adjusted AFS =

(High-Risk % × High-Risk AFS) + (Low-Risk % × Low-Risk AFS)

where Low-Risk AFS = Adjustment Factor × High-Risk AFS

A meta-analytic average of the risk-adjusted AFS rates was then calculated using inverse variance weighting and a random-effects approach to account for the variability in the estimates and the potential heterogeneity of the studies; 95% confidence intervals (CIs) around the meta-analytic average risk-adjusted AFS rate were also calculated.

TABLE 3. Unadjusted and risk-adjusted amputation-free survival rates at 6 months.

Study	Pts (n)	Event-Free Survivors (n)	Unadjusted AFS Rate	Included RCs	Observed Proportion RC 4	Observed Proportion RC 5/6	Imputed Proportion RC 5/6	Risk-Adjusted AFS Rate
Brass et al. 2006[32]	177	146	82.5%	4, 5, 6	NR	NR	66.9%	59.3%
Teraa et al. 2015[33]	79	66	83.5%	3, 4, 5, 6	31.6%	63.3%	NA	58.3%
Dubsky et al. 2013[34]	22	10	45.5%	4, 5, 6	NR	NR	66.9%	32.7%
Iafrati et al. 2016[35]	34	22	64.7%	5	0.0%	100.0%	NA	64.7%
Anghel et al. 2011[36]	14	3	21.4%	4,5	50.0%	50.0%	NA	13.5%
Li et al. 2013[37]	29	23	79.3%	4, 5, 6	NR	NR	66.9%	57.0%
Benoit et al. 2011[38]	14	9	64.3%	4,5	50.0%	50.0%	NA	40.4%
Gupta et al. 2013[39]	10	8	80.0%	4, 5, 6	20.0%	80.0%	NA	64.7%
Szabo et al. 2013[40]	10	4	40.0%	4, 5, 6	NR	NR	66.9%	28.8%
Belch et al. 2011[41]	259	196	75.7%	4, 5, 6	NR	NR	66.9%	54.4%
Losordo et al. 2012[42]	12	8	66.7%	4,5	41.7%	58.3%	NA	44.7%
Nikol et al. 2008[43]	56	34	60.7%	4, 5, 6	NR	NR	66.9%	43.7%
Powell et al. 2012[44]	24	17	70.8%	4, 5, 6	NR	NR	66.9%	50.9%
Idei et al. 2011[45]	30	3	10.0%	4, 5, 6	27.0%	73.0%	NA	7.6%
Pignon et al. 2017[46]	19	14	73.7%	4,5	35.0%	65.0%	NA	52.1%
Wang et al. 2018[47]	36	28	77.8%	4,5	66.7%	33.3%	NA	43.5%
Faglia et al. 2010[48]	27	3	11.1%	4,5,6	37.0%	63.0%	NA	7.7%
Dalla Paola et al. 2019[49]	84	50	59.5%	4,5,6	NR	NR	66.9%	42.8%
Dubsky et al. 2019[50]	44	31	70.5%	4,5,6	NR	NR	66.9%	50.7%
Faglia et al. 2012[51]	12	3	25.0%	5.6	0.0%	100.0%	NA	25.0%
		Meta-Analytic Average	58.6%			Meta-Analytic Average		42.0%
		95% Confidence Interval	47.6-69.5			95% Confidence Interval		32.8-51.2

NA = not applicable; NR = not reported; RC = Rutherford category.

Results

Study characteristics. The literature search resulted in a total of 1307 publications. After screening and eligibility assessment for inclusion criteria, a total of 32 studies were selected and included in the meta-analysis (**Figure 1**). Of these, 28 reported outcomes at 6 months (**Supplemental Table S4**) and 24 reported outcomes at 12 months (**Supplemental Table S5**).

The supplemental literature search undertaken for the purposes of risk adjustment resulted in 290 publications. After screening and eligibility assessment, 3 studies were selected (**Supplemental Figure S1**).

Quality of evidence. The quality of study design and potential risk for bias is included in **Supplemental Table S6**. Some studies had high risk of bias due to either random sequence generation, allocation concealment, blinding of participants and personnel, and/or blinding of outcome assessments. No studies were at high risk for incomplete outcome data or selective reporting.

Overall AFS event rates and temporal trends. Overall, the unadjusted meta-analytic average AFS rate in all identified studies was 56.0% at 6 months (**Supplemental Table S4**) and 47.5% at 12 months (**Supplemental Table S5**). An analysis by time of enrollment determined that AFS rate was significantly higher in studies enrolling patients after 2003 at both 6 months (20 studies; n = 992) and 12 months (18 studies; n = 901) compared with AFS rate reported before 2003 at 6 months (8 studies; n = 449) and 12 months (6 studies; n = 463) (weighted averages at 6 months, 68.3% vs 48.3% [*P*<.001] and at 12 months, 57.2% vs 47.3% [*P*<.001]) (**Table 1**). There was no statistically significant difference at 6 or 12 months when studies reporting AFS were grouped into those ending enrollment between 2003-2010 compared with those ending in 2010 and later (**Table 1**). Therefore,

TABLE 4. Unadjusted and risk-adjusted amputation-free survival rates at 12 months.

Study	Pts (n)	Event-Free Survivors (n)	Unadjusted AFS Rate	Included Rutherford Categories	Observed Proportion RC 4	Observed Proportion RC 5/6	Imputed Proportion RC 5/6	Risk-Adjusted AFS Rate
Marston et al. 2006[52]	142	105	73.9%	4, 5, 6	NR	NR	60.3%	50.3%
Nikol et al. 2008[44]	56	27	48.2%	4, 5, 6	NR	NR	60.3%	32.8%
Belch et al. 2011[41]	259	173	66.8%	4, 5, 6	NR	NR	60.3%	45.5%
Losordo et al. 2012[42]	12	6	50.0%	4,5	41.7%	58.3%	NA	33.5%
Teraa et al. 2015[33]	79	53	67.1%	3, 4, 5, 6	31.6%	63.3%	NA	46.8%
Raval et al. 2014[53]	3	1	33.3%	4, 5, 6	NR	NR	60.3%	22.7%
Powell et al. 2012[44]	24	16	66.7%	4, 5, 6	NR	NR	60.3%	45.4%
Benoit et al. 2011[38]	14	9	64.3%	4,5	50.0%	50.0%	NA	40.4%
Kibbe et al. 2016[54]	11	9	81.8%	4, 5	63.6%	36.4%	NA	46.7%
Idei et al. 2011[45]	30	0	0.0%	4, 5, 6	27.0%	73.0%	NA	0.0%
Szabo et al. 2013[40]	10	4	40.0%	4, 5, 6	NR	NR	60.3%	27.2%
Pignon et al. 2017[46]	19	14	73.7%	4, 5	35.0%	65.0%	NA	52.1%
Wang et al. 2018[47]	36	25	69.4%	4,5	66.7%	33.3%	NA	38.8%
Faglia et al. 2010[48]	27	1	3.7%	4,5,6	37.0%	63.0%	NA	2.6%
Dalla Paola et al. 2019[49]	84	29	34.5%	4,5,6	NR	NR	60.3%	23.5%
Dubsky et al. 2019[50]	44	23	52.3%	4,5,6	NR	NR	60.3%	35.6%
Faglia et al. 2012[51]	12	3	25.0%	5.6	0.0%	100.0%	NA	25.0%
Meta-Analytic Average			50.3%				Meta-Analytic Average	33.3%
95% Confidence Interval			33.6-67.0				95% Confidence Interval	21.1-45.5

NA = not applicable; NR = not reported; RC = Rutherford category.

subsequent analyses with risk adjustment for RC considered only studies with enrollment ending in 2003 and later. There were 20 studies for 6-month AFS analysis (n = 992) and 17 studies (n = 862) for 12-month AFS analysis.

Risk-adjusted AFS rates. Based on unadjusted HRs of RC 4 vs RC 5/6 patients (**Table 2**), a calculated AFS adjustment factor of 2.18 was applied to derive risk-adjusted 6- and 12-month AFS rates in the population of interest (see Methods). Unadjusted and risk-adjusted 6- and 12-month AFS rates for each study, along with relevant population characteristics, are summarized in **Table 3** and **Table 4**. RC was reported in 11/20 studies reporting 6-month AFS rates and 9/17 studies reporting 12-month AFS rates after 2003. The average proportion of RC 5/6 patients was imputed at 66.9% for 6-month AFS studies and 60.3% for 12-month AFS studies based on the average of all studies that reported this proportion.

The unadjusted meta-analytic estimate of AFS in studies ending enrollment after 2003 was 58.6% (95% CI, 47.6-69.5) at 6 months, and 50.3% (95% CI, 33.6-67.0) at 12 months. After risk adjustment, the meta-analytic estimate of AFS at 6 months was 42.0% (95% CI, 32.8-51.2) and at 12 months was 33.3% (95% CI, 21.1-45.5) (**Table 3** and **Table 4**).

Discussion

This is the first systematic review and meta-analysis of the outcomes of patients with RC 5/6 CLI who were poor candidates for conventional surgical or endovascular revascularization approaches. There are several important conclusions from our study. The most relevant finding is the low rates of AFS in this population; based on best estimates, more than 60% of patients with RC 5/6 will either lose a limb or die within 1 year. The implications are sobering given that the prevalence of CLI continues to rise with current increasing life expectancy, prevalence of diabetes, obesity, and sedentary lifestyles.[1,12]

Despite these dismal statistics, these "contemporary" outcomes represent an improvement for no-option CLI patients relative to similar patients enrolled before 2003. These observations likely represent the impact of changes in secondary prevention guidelines with the introduction of new therapies for lipid-lowering and favorable trends reported in usage of

lipid-lowering medications and decrease trans-fatty acids consumption,[13] the 2003 introduction of JNC-7 hypertension management guidelines,[14] smoking cessation recommendation,[15] and no-smoking laws that became more widespread in 2004. The current Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC II) guidelines recommend intensified medical management for all patients with PAD, to include smoking cessation, weight reduction, lipid lowering, antihypertensives, diabetic control, and antiplatelet therapy. While endovascular techniques such as percutaneous transluminal angioplasty (PTA) are the preferred treatment for limited infrainguinal disease (stenoses/occlusions up to 10 cm in length) and infrapopliteal limb salvage, surgical and endovascular options are generally limited by anatomic considerations, leaving many patients without options for either conventional approach. The recommended treatment approaches for no-option CLI are limited, with no clear gold standard. Retrograde access, transcollateral recanalization, and pedal-plantar loop techniques have provided successful options in patients with failed conventional revascularization.[16-18] A recent meta-analysis of randomized controlled trials found that bone-marrow derived cell therapy provided no benefit for amputation, survival, or AFS in patients with CLI.[19] However, the studies included in the meta-analysis were small in size, mostly pilot studies, and insufficiently powered for therapeutic efficacy. Intermittent pneumatic compression (arterial flow pump) has been shown in single-center retrospective registries to reduce amputation rates in patients without revascularization options; however, the quality of evidence is weak.[20]

It has been estimated that 5%-20% of CLI patients are not candidates for conventional surgical or endovascular revascularization,[5-7] and despite optimal medical therapy, current outcomes remain dismal and emphasize the clinical need for new therapeutic approaches. Novel revascularization options under development, such as total percutaneous bypass [21] and total percutaneous deep-vein arterialization,[22] may offer safe and effective options for patients who otherwise have none. The results of the present meta-analysis may help inform the evaluation of these technologies, as exemplified by a recent cost-effectiveness analysis conducted by Pietszch et al.[23]

Study limitations. Our systematic review and meta-analysis has several limitations. Sample sizes in the identified studies were generally small, and definitions and classifications of CLI and the clinical and anatomic determinants of unsuitability for revascularization varied. Due to incomplete reporting of enrollment dates and the proportion of patients in each risk category, some missing data were imputed based on best available information. Newer classification systems, such as the Society for Vascular Surgery Lower Extremity Threatened Limb Classification: Risk stratification based on Wound, Ischemia, and foot Infection (WIfI), may provide improved prognostic value in high-risk patients, but lack external validation in a large dataset.[24] However, these measures were not reported in our source data, and challenges remain, including selection of the appropriate hemodynamic cutoffs[25,26] and infrequent reporting of ankle-brachial indexes in clinical settings.[27] Lastly, our primary outcome of AFS does not align with recent recommendations from the Society of Vascular Surgery CLI Working Group for endpoints in a population of patients with CLI,[28] although the relevance of the composite major adverse limb events (which includes reintervention and early intervention-related complications) is inherently limited in the no-option patient population presented in this report.

Conclusion

Our study re-emphasizes the dismal outcomes for patients with advanced CLI who are not candidates for currently available endovascular or surgical revascularization approaches. Given the increasing prevalence of peripheral vascular disease and CLI, new approaches to enable revascularization in this high-risk population are sorely needed.

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Supplemental Materials

SUPPLEMENTAL TABLE S1. Search terms for 6-month and 12-month outcomes. The table contains an abridged search strategy used for OVID querying Medline, EMBASE, and the Cochrane Database of Systematic Reviews (CDSR).

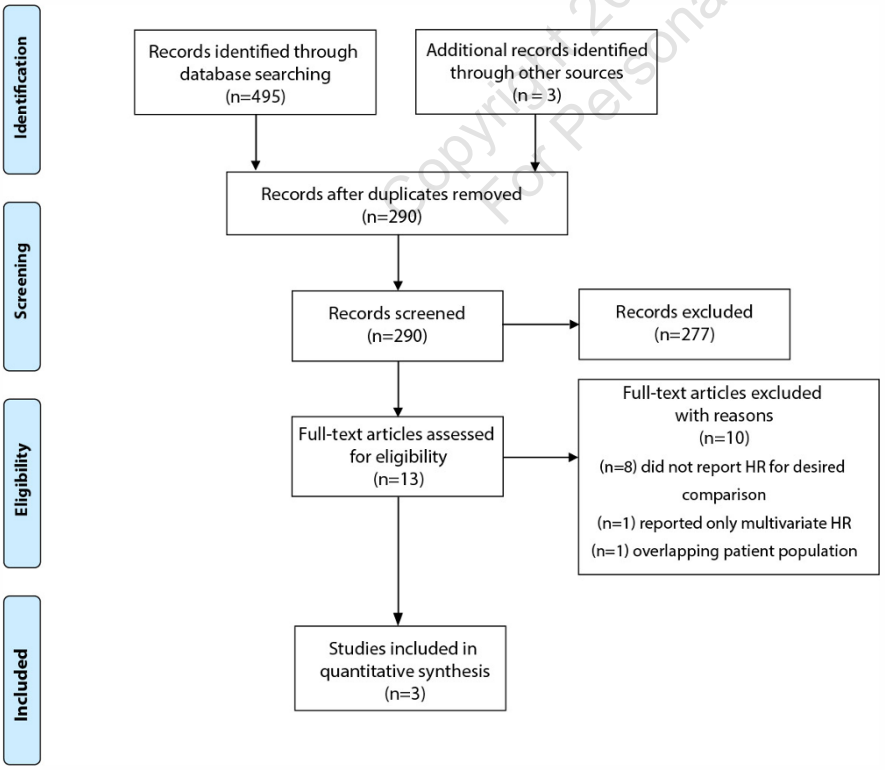
Search ID	Search Terms
1.1	peripheral artery disease OR peripheral occlusive disease OR peripheral vascular disease OR peripheral angiopathy OR atherosclerosis OR arteriosclerosis OR intermittent claudication OR arterial occlusive diseases OR ischemia OR ischaemia OR ischemic OR ischaemic OR "circulation disorder*" OR "circulation failure*" OR "circulation disturbance*" OR "circulatory disorder*" OR "circulatory failure*" OR "circulatory disturbance* OR ((artery OR vascular OR vein OR peripheral) AND (stenosis OR lesion OR blockage OR occlusion OR obstruction))
1.2	leg OR lower extremity OR foot OR feet OR toes OR digits OR knees OR ankle OR calf
1.3	mortality OR survival OR amputation OR amputation-free survival OR limb loss OR wound healing OR ulcer healing
1.4	natural history OR placebo OR critical OR severe OR untreated OR unreconstructed OR nonreconstructable OR unintervened OR unsuitable for surgery OR unsuitable for revascularization OR no-option
1.5	[study type] controlled OR randomized OR meta-analysis OR systematic review OR guideline OR case control OR follow-up OR cohort OR longitudinal OR prospective OR retrospective OR observational OR comparative OR clinical trial OR evaluation OR validation OR experimental OR evaluation
1.6	1.1 AND 1.2 AND 1.3 AND 1.4 AND 1.5
1.7	1.8 AND humans AND English

SUPPLEMENTAL TABLE S2. Search terms for risk adjustment. The table contains an abridged search strategy used for OVID querying Medline, EMBASE, and the Cochrane Database of Systematic Reviews (CDSR).

Search ID	Search Terms
2.1	"amputation-free survival" or "AFS" or "death or major amputation" or "death or amputation" or "major amputation" or "mortality" or "death" or "all-cause" or "limb salvage"
2.2	"Rutherford" or "Fontaine"
2.3	2.1 and 2.2
2.4	"CLI" or "critical limb ischemia" or "PVD" or "peripheral vascular disease" or "rest-pain" or "peripheral art*" or "ischemia" or "lower extremity ischemia" or "lower limb ischemia"
2.5	2.3 and 2.4
2.6	"*ratio" or "*variate" or "predic*" or "hazard" or "Cox proportional hazard*"
2.7	2.6 AND humans AND English

SUPPLEMENTAL TABLE S3. Rutherford categorization based on reported objective criteria.

Grade	Category	Clinical Criteria	Objective Criteria
0	0	Asymptomatic, no hemodynamically significant occlusive disease	Normal treadmill or reactive hyperemia test
	1	Mild claudication	Completes treadmill exercise; ankle pressure after exercise >50 mm Hg but at least 20 mm Hg lower than resting value
I	2	Moderate claudication	Between categories 1 and 3
	3	Severe claudication	Cannot complete standard treadmill exercise, and ankle pressure after exercise <50 mm Hg
II	4	Ischemic rest pain	Resting ankle pressure <40 mm Hg, flat or barely pulsatile ankle or metatarsal pulse-volume recording; toe pressure <30 mm Hg
III	5	Minor tissue loss, non-healing ulcer, focal gangrene with diffuse pedal ischemia	Resting ankle pressure <60 mm Hg, ankle or metatarsal pulse-volume recording flat or barely pulsatile; toe pressure <40 mm Hg
	6	Major tissue loss, extending above thrombomodulin level, functional foot no longer salvageable	Same as category 5



SUPPLEMENTAL FIGURE S1. PRISMA flow diagram for supplemental literature search. HR = hazard ratio.

SUPPLEMENTAL TABLE S4. Studies reporting amputation-free survival rates at 6 months in "no-option" critical limb ischemia patients.*

Study*	Patients (n)	Enrollment End	Event-Free Survivors (n)	Event-Free Rate
Lepantalo et al. 1996[1]	105	Jul 1992	40	38.1%
Boccalon et al. 2000[2] (cohort A)	62	Jul 2000	32	51.6%
Brass et al. 2006[3]	177	Sep 2005	146	82.5%
Teraa et al. 2015[4]	79	Jun 2012	66	83.5%
Dubsky et al. 2013[5]	22	Mar 2012	10	45.5%
Iafrati et al. 2016[6]	34	Jul 2016	22	64.7%
Belch et al. 2011[7]	37	Feb 1994	20	54.1%
Jivegard et al. 1995[8]	26	Jul 1995	16	61.5%
Klomp et al. 1999[9]	60	Jul 1996	34	56.7%
Lund et al. 1999[10]	28	Jun 1999	10	35.7%
Anghel et al. 2011[11]	14	Mar 2011	3	21.4%
Li et al. 2013[12]	29	Jan 2010	23	79.3%
Benoit et al. 2011[13]	14	Aug 2011	9	64.3%
Gupta et al. 2013[14]	10	Jul 2012	8	80.0%
Bliss et al. 1991[15]	71	Jul 1991	30	42.3%
Pignon et al. 2017[16]	19	Jul 2009	14	73.7%
Szabo et al. 2013[17]	10	Oct 2013	4	40.0%
Belch et al. 2011[18]	259	Jul 2009	196	75.7%
Losordo et al. 2012[19]	12	Apr 2010	8	66.7%
Nikol et al. 2008[20]	56	Apr 2004	34	60.7%
Powell et al. 2012[21]	24	Mar 2010	17	70.8%
Idei et al. 2011[22]	30	Dec 2008	3	10.0%
Ubbink et al. 1999[23]	60	May 1994	35	58.3%
Wang et al. 2018[24]	36	Jan 2018	28	77.8%
Faglia et al. 2010[25]	27	Dec 2003	3	11.1%
Dalla Paola et al. 2019[26]	84	Oct 2017	50	59.5%
Dubsky et al. 2019[27]	44	Jul 2016	31	70.5%
Faglia et al. 2012[28]	12	Dec 2009	3	25.0%
			Simple Average	55.7%
			Weighted Average	62.1%
			Meta-Analytic Average	56.0%
			95% Confidence Interval	47.4-64.6

*Reference numbers refer to Supplemental Reference list.

SUPPLEMENTAL TABLE S5. Studies reporting amputation-free survival rates at 12-months in "no-option" critical limb ischemia patients.*

Study	Total Patients (n)	Enrollment End	Event-Free Survivors (n)	Event-Free Rate
Lepantalo et al. 1996[1]	105	Jul 1992	30	28.6%
Marston et al. 2006[29]	142	Mar 2005	105	73.9%
Boccalon et al. 2000[2] (cohort B)	207	Jul 2000	133	64.3%
Nikol et al. 2008[20]	56	Apr 2004	27	48.2%
Belch et al. 2011[18]	259	Jul 2009	173	66.8%
Losordo et al. 2012[19]	12	Apr 2010	6	50.0%
Teraa et al. 2015[4]	79	Jun 2012	53	67.1%
Belch et al. 2011[7]	37	Feb 1994	15	40.5%
Jivegard et al. 1995[8]	26	Jul 1995	13	50.0%
Lund et al. 1999[10]	28	Jun 1999	6	21.4%
Raval et al. 2014[30]	3	Aug 2012	1	33.3%
Powell et al. 2012[21]	24	Mar 2010	16	66.7%
Amann et al. 2003[31]	39	Jan 2002	18	44.9%
Benoit et al. 2011[13]	14	Aug 2011	9	64.3%
Kibbe et al. 2016[32]	11	Jul 2012	9	81.8%
Idei et al. 2011[22]	30	Dec 2008	0	0.0%
Pignon et al. 2017[16]	19	Jul 2009	14	73.7%
Szabo et al. 2013[17]	10	Oct 2013	4	40.0%
Ubbink et al. 1999[23]	60	May 1994	22	36.7%
Wang et al. 2018[24]	36	Jan 2018	25	69.4%
Faglia et al. 2010[25]	27	Dec 2003	1	3.7%
Dalla Paola et al. 2019[26]	84	Oct 2017	29	34.5%
Dubsky et al. 2019[27]	44	Jul 2016	23	52.3%
Faglia et al. 2012[28]	12	Dec 2009	3	25.0%
			Simple Average	47.4%
			Weighted Average	53.8%
			Meta-Analytic Average	47.5%
			95% Confidence Interval	35.1-59.8

*Reference numbers refer to Supplemental Reference list.

SUPPLEMENTAL TABLE S6. Risk of bias assessment.

Study*	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias
Lepantalo et al. 1996[1]	–	–	–	–	+	+	+
Boccalon et al. 2000[2] (cohort A)	+	+	+	+	+	+	+
Brass et al. 2006[3]	+	+	+	+	+	+	+
Teraa et al. 2015[4]	+	+	+	+	+	+	+
Dubsky et al. 2013[5]	–	–	–	–	+	+	+
Iafrati et al. 2016[6]	+	+	+	+	+	+	+
Belch et al. 2011[7]	+	+	+	+	+	+	+
Jivegard et al. 1995[8]	+	–	–	?	+	+	+
Klomp et al. 1999[9]	+	–	–	?	+	+	+
Lund et al. 1999[10]	–	–	–	–	?	+	?
Anghel et al. 2011[11]	+	+	+	+	+	+	+
Li et al. 2013[12]	+	+	+	–	+	+	+
Benoit et al. 2011[13]	+	+	+	+	+	+	+
Gupta et al. 2013[14]	+	+	+	+	+	+	+
Bliss et al. 1991[15]	+	+	+	+	+	+	+
Pignon et al. 2017[16]	+	+	+	+	+	+	+
Szabo et al. 2013[17]	+	+	?	?	+	+	?
Belch et al. 2011[18]	+	+	+	+	+	+	+
Losordo et al. 2012[19]	+	+	+	+	+	+	+
Nikol et al. 2008[20]	+	+	+	+	+	+	+
Idei et al. 2011[22]	–	–	?	?	+	+	?
Ubbink et al. 1999[23]	+	–	?	?	+	+	?
Marston et al. 2006[29]	–	–	–	–	+	+	+
Raval et al. 2014[30]	+	+	+	+	+	+	+
Amann et al. 2003[31]	–	–	–	–	+	+	?
Kibbe et al. 2016[32]	+	+	+	+	+	+	+
Wang et al. 2018[24]	+	+	+	+	+	+	+
Faglia et al. 2010[25]	–	–	–	–	+	+	+
Dalla Paola et al. 2019[26]	–	–	–	–	+	+	+
Dubsky et al. 2019[27]	+	+	+	+	+	+	+
Faglia et al. 2012[28]	–	–	–	–	+	+	+

+ = low-risk
– = high-risk
? = uncertain risk
*Reference numbers refer to Supplemental Reference list.

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When "No Options" is No Longer an Option: Moving the Needle Forward in Advanced Stage Critical Limb Ischemia

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Despite significant advances in the diagnosis and treatment of peripheral arterial disease (PAD), the incidence remains remarkably high and increasing worldwide.[1] In part, this is due to the fact that the clinical course and management of PAD remains understudied and underfunded in comparison with cardiovascular and cerebrovascular conditions. The individual-level and population-level economic burden of PAD and critical limb ischemia mandates further understanding, as the cost of care is approaching nearly $6.1 billion in the United States alone.[2] Notably, the vast majority of costs are incurred by patients with advanced stage disease, in particular, critical limb ischemia with tissue loss. Although peripheral vascular revascularization rates have increased in the past decade, both due to refinement in technique and the development of new technology, amputation rates remain high.[3] Amputation is one of the most morbid and fatal sequelae of cardiovascular disease, with an immediate impact on quality of life and prognosis on par with the most advanced cancers.[4]

The current study[5] curates and centralizes a significant amount of work that sheds light on the overall dismal clinical course of patients with Rutherford category 5 and 6 PAD and "no options" for revascularization. In this meta-analysis, Ghare et al[5] compiled 32 studies of more than 1400 Rutherford[4,6,7] patients that examine outcomes after they were deemed to have no revascularization options, making this the largest single piece of work examining this patient population. The primary endpoint evaluated was amputation-free survival (AFS) at either 6 or 12 months. The authors found that AFS increased significantly after 2003 at both 6- and 12-month intervals (48.3% vs 68.3% after 2003 and 47.3% vs 57.2% after 2003, respectively), but remained similar between 2003-2010 and 2010-present, potentially reflecting an initial stepwise improvement in medical or interventional therapy that has now plateaued. After risk adjustment accounting for the slightly lower risk of Rutherford category 4 patients included in some studies, the investigators found an AFS rate of 42.0% at 6 months and 33.3% at 12 months. The study overall demonstrates that among patients with severe disease who have progressed past medical management and traditional revascularization options, we still have a long way to go to make a meaningful impact on reducing amputation rates and improving survival.

A key tenet that arises from this study is the necessity for early detection and intensive medical management, as this is likely the single most effective way to reduce the burden of not only amputations, but PAD as an entity. While the most effective known interventions are lifestyle changes (ie, smoking cessation, exercise therapy, and comorbidity management) and aggressive medical management with statins and antiplatelets, there remain significant barriers to achieving these goals, especially in regard to patient awareness.[6,7] The lack of support for routine ankle-brachial index screening of high-risk patients has remained a major obstacle to improving the opportunity to implement early preventative measures for those at risk of PAD and amputation.[8] This recommendation against screening contradicts supportive randomized trial data.[9] Furthermore, our efforts at optimizing medical and lifestyle therapies among those with known PAD have been met with marginal success. For instance, in patients with diagnosed PAD who remain smokers, only 35% of patients receive counseling or medication. In addition, among all patients diagnosed with PAD, as few as 33% are taking statins despite the well-known benefits of these therapies.[10] In addition to appropriate pharmacologic management, supervised exercise therapy is well established at improving symptoms of stable PAD and cardiovascular conditioning, yet many physicians have never referred patients to a supervised exercise program and nearly a third of physicians surveyed did not know whether CMS reimburses for exercise therapy.[6,11] This has resulted in dismal utilization, as highlighted by a recent assessment of Medicare data demonstrating that only 1.3% of insured patients diagnosed with claudication were enrolled in supervised exercise therapy.[12]

On the other end of the spectrum, the population of patients deemed to have no revascularization options is continuing to shrink. Multidisciplinary, standardized strategies to approach limb care for patients deemed to have no-option critical limb ischemia have resulted in improvements in 1-year limb-salvage rates.[13] Furthermore, novel techniques to improve limb flow have provided additional opportunities for these patients to delay or avoid amputation. In particular, the recent re-emergence of deep vein arterialization has created a treatment opportunity for many patients traditionally deemed to have no revascularization options. The LimFlow device, which arterializes the peroneal vein at the tibioperoneal trunk, has yielded amputation-free

survival rates of 83% at 6 months and 67% at 24 months in patients with Rutherford categories 5 and 6 disease, as well as achieving complete wound healing in 73% of all treated patients.[14] As this procedure continues to be refined, it has the opportunity to make a substantial impact on limb-salvage rates.

As we progress through this next decade, it is critical that we invest in preventative care, foster the implementation of multidisciplinary and multidimensional therapeutic strategies into routine PAD practice, and promote the development of new technologies for revascularization in order to improve the long-term outcomes for this complex patient population. With time and investment, we may be able to retire the term "no option" and finally move the needle forward on reducing amputations.

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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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Key words: critical limb ischemia, peripheral vascular disease, peripheral artery disease

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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Novel Chronic Total Occlusion Scoring System in Predicting Outcome: Is it Ready for PRIME Time?

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In this issue of the *Journal of Critical Limb Ischemia*, Mustapha et al analyzed multicenter data in patients with symptomatic peripheral vascular disease (PVD)/critical limb ischemia (CLI) in relation to the presence and location of chronic total occlusion (CTO).[1] Besides usual patient characteristics, such as risk factors and comorbidities, lesions were also graded according to the novel PRIME scoring system, together with lesion characteristics, such as length and calcification.

While endovascular treatment has been shown to be efficacious in the treatment of CLI and is widely adopted as a first-line treatment option, the relationship between lesion characteristics and their impact of limb salvage and mortality has not been adequately addressed.[2] To this end, CTO (compared with non-CTO disease) presents not only as a technical challenge, but likely represents more severe underlying systemic disease, chronicity, more-profound ischemia, and the end stage of the CLI spectrum, with the attendant mortality and limb-loss implications.

The study population resembles a real-world practice with an elderly population (mean age, 69.9 years) and with the majority exhibiting risk factors, such as hypertension, dyslipidemia, diabetes, and coronary artery disease. While the number of dialysis-dependent patients is low (5.4%), more than half of the study population had renal impairment of stage 3A and higher. Additionally, the high proportion of calcification (86.0%) and long lesion lengths (mean, 200 mm) is reflective of the real-world experience in such a population.

The authors found significant increased 1-year survival in patients with above-the-knee (ATK)-CTO (PRIME 1 and 2) vs multilevel (PRIME 3 and 6) and below-the-knee (BTK)-CTO (PRIME 4 and 5) (97.1% vs 86.2% vs 83.6%, respectively).[1] This is in part due to the older age and significantly higher incidence of diabetes and end-stage renal failure in patients with BTK-CTOs.[1] However, it also reflects that more extensive disease (multilevel) and more distal disease (BTK-CTO) portends a different disease trajectory. The findings are consistent with the 2 meta-analyses by Katsanos et al, which indicated that all-cause death at 1 year was higher in patients with infrapopliteal disease vs femoropopliteal disease (8.0% vs 2.3%, respectively).[3,4]

The authors also reported that patients with BTK-CTOs had a higher 1-year amputation rate compared with patients with ATK-CTOs (10% vs 1%, respectively).[1] One could postulate that the higher incidence of diabetes and end-stage renal failure in patients with BTK-CTOs predisposes this group to concomitant small artery disease (SAD). Ferraresi et al found that these patients are susceptible to SAD (disease involving pedal-plantar arch and small arteries arising from it), resulting in the failure of the "distribution" system of the foot.[5] Rashid et al showed that the quality of pedal arch positively impacted wound healing and time to healing after open surgical infrapopliteal bypass.[6] Similarly, Troisi et al showed pedal arch status also positively impacted time to healing, limb salvage, and survival in diabetic patients with foot wounds undergoing infrainguinal endovascular revascularization.[7] In the presence of SAD, reconstitution of flow to the wound-angiosome is crucial for healing as the failure of the distribution system isolates every angiosome, which would impact wound healing.

In conclusion, the authors should be congratulated in highlighting that location and extent of CTO are unique risk factors with definite impact in the context of endovascular treatment of CLI. The data presented suggest that more distal and more extensive disease portends a different trajectory than more proximal disease, and this knowledge could be utilized in patient risk stratification, treatment strategy development, and future trial designs.

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Comparison Between Intra-Arterial Carbon Dioxide and Iodinated Contrast Agent Injections in Patients With Lower-Limb Peripheral Arterial Diseases and Mild-to-Moderate Renal Dysfunction: A Randomized Controlled Trial

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Abstract

Background. This randomized, controlled trial was designed to compare the rate of postangiographic contrast-induced nephropathy (CIN) between the intra-arterial injections of carbon dioxide (CO_2) and the iodinated contrast agent (ICA). The study population was chosen to investigate the direct toxicity of the ICA while eliminating the role of catheter manipulation and the resultant microembolization as a confounding cause of CIN. **Methods.** Candidates for lower-limb endovascular procedures with a baseline glomerular filtration rate exceeding 30 mL/min/1.73 m^2 were randomized into CO_2 and ICA angiography groups. The primary endpoint of this study was the occurrence of CIN, defined as an elevation in baseline serum creatinine exceeding 25% or 0.5 mg/dL within 72 hours after the procedure. **Results.** The study population comprised 110 patients: 57 in the ICA group and 53 in the CO_2 group. The incidence of CIN was significant in the ICA group compared with the CO_2 group (13 [22.8%] vs 4 [7.5%], respectively; *P*=.03). Our multivariate regression analysis determined ICA volume to be a significant predictor of CIN. **Conclusion.** In the present study, which was performed on patients undergoing lower-limb endovascular procedures with mild-to-moderate renal dysfunction, CO_2 angiography decreased CIN incidence. The ICA volume was an important predictor of CIN in the absence of microembolization.

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Key words: carbon dioxide angiography, contrast-induced nephropathy, digital subtraction angiography, peripheral arterial disease

Contrast-induced nephropathy (CIN) is a postprocedural rise in creatinine of >25% above the baseline.[1] CIN is a well-recognized complication of diagnostic angiography or percutaneous and coronary interventions, and it can increase not only morbidity and mortality rates but also healthcare costs.[1,2] The prevalence of CIN is reported to range between 1% and 45% according to comorbidities in various populations and different definitions in studies.[3] CIN is among the most common etiologies of hospital-acquired renal insufficiency,[4] with high in-hospital and 12-month direct healthcare costs.[5] Indeed, CIN increases in-hospital mortality (odds ratio, 5.5), with 1-year mortality rising among patients whether they require dialysis or not (45.2% and 35.4%, respectively).[6]

CIN usually occurs within 24 to 72 hours after the administration of the iodinated contrast agent (ICA).[7] Conditions such as chronic kidney disease, diabetes, congestive heart failure, anemia, increased age, cirrhosis, non-steroidal anti-inflammatory drug or diuretic consumption, proteinuria, dehydration, peripheral artery disease, and hypertension could increase the risk of CIN.[8,9]

The plausible mechanisms of CIN include the direct toxicity of the ICA on nephrons and catheter manipulations in the arterial system upstream from the renal arteries, causing microembolic showers into the renal arteries.[8-13] The cited etiologies are bolstered by reports of higher rates of CIN in patients who undergo intra-arterial ICA injection or angiography via femoral access, in which the risk of CIN increases due to catheter manipulation.[12,14] Theoretically, carbon dioxide (CO_2) does not cause renal toxicity directly; hence, the increasing popularity of CO_2 use as an alternative to the ICA in diagnostic and endovascular procedures in both venous and arterial systems below the diaphragm.[15,16] In the present study, we sought to compare intra-arterial CO_2 and ICA injections in terms of their effects on the incidence of CIN in patients undergoing infrainguinal endovascular procedures.

Methods

Study design. The present study is a single-center, open-label, parallel, randomized controlled trial. The participants were randomly assigned to 2 contrast-type groups: CO_2 and the ICA. Randomization was performed with a web-based system via the simple random sampling method and allocation sequence concealment. All the patients provided written informed consent, and the study protocol complied with the Declaration of Helsinki. The study was approved by the ethics committee of Rajaie Cardiovascular Medical and Research Center (Ethic ID: IR.RHC.REC.1398.055), and it was registered in the Iranian Registry of Clinical Trials (IRCT 20191107045359N1).

Study population. All candidates for peripheral lower-limb angiography older than 18 years of age and with a baseline glomerular filtration rate (GFR) of >30 mL/min/1.73 m² based on the Modification of Diet in Renal Disease (MDRD) equation were considered eligible for recruitment in the study. The exclusion criteria were a history of contrast exposure in the preceding 30 days, heart or kidney transplantation, proteinuria, or cirrhosis; chronic hemodialysis fluctuations in serum creatinine levels exceeding 15% in the preceding 2 days; the presence of intracardiac shunts; and the need for catheterization higher than the renal arteries including antegrade upper limb access (radial or brachial arteries). For the prevention of confounding effects, patients allocated to the CO_2 group who might need the administration of >20 mL of the ICA based on the results of a previous study[17] were also excluded from this study.

Study interventions. According to the contrast medium selected for the procedure, the study patients were randomized into a CO_2 group and an ICA group. A low-osmolar ICA diluted at a minimum 1:3 ratio was used for the current study. Automated injection (Angiodroid SRL) was employed for CO_2 angiography. The preprocedural work-up included thorough clinical examination, complete blood count, and baseline biochemical examination (the levels of blood urea nitrogen, serum creatinine, blood glucose, sodium, and potassium, as well as the prothrombin time). A unified protocol was drawn upon for hydration in both groups. Both groups were hydrated based on the left ventricular ejection fraction (LVEF) in the period starting 12 hours before and 6 hours after the procedure. Intravenous saline (0.9%) was administered at a rate of 1 mL/kg/h to patients with LVEFs >30% and at a rate of 0.5 mL/kg/h to those with LVEFs ≤30%. All procedures were performed below the renal arteries via lower-limb access sites, including retrograde common femoral access with the conversion potential to crossover access for angiography or endovascular management on the contralateral limbs, antegrade femoral access, retrograde pedal access, and popliteal access. For the prevention of microembolic showers in the renal arteries during the crossover technique, special measures were taken to maintain catheters and sheets below the renal arteries. Both ICA and CO_2 angiography procedures were performed under mild sedation. Blood urea nitrogen and serum creatinine were measured 72 hours after the procedure.

Study endpoints. The primary endpoint of this study was the occurrence of CIN, defined as a rise in baseline serum creatinine exceeding 25% or 0.5 mg/dL within 72 hours after the procedure. The secondary endpoint was death or the need for kidney replacement therapy during a 1-month follow-up period. Limb or abdominal pain due to CO_2 injection was also recorded.

Statistical analysis. The fitness of interval variables to normal distribution was assessed via the 1-sample Kolmogorov–Smirnov test. The data were described as mean ± standard deviation for continuous variables and as frequencies (percentages) for nominal variables. Comparisons between the 2 study groups were performed using the independent sample t-test for interval variables and the Pearson Chi-square or Fisher's exact test for categorical variables. A multivariate analysis was applied through a binary logistic regression model to investigate the adjusted association between CIN and the intra-arterial injection of CO_2 or the ICA. A *P*-value of <.05 was considered statistically significant. The statistical analyses were performed with IBM SPSS Statistics, version 22, for Windows (IBM, Inc).

Results

The study population comprised 110 patients who were randomly divided into the ICA group (n = 57) and the CO_2 group (n = 53). The participants' demographic, clinical, and procedural characteristics are summarized in **Table 1**. Except for baseline creatinine, which was significantly higher in the CO_2 group (1.46 ± 0.45 mg/dL vs 1.13 ± 0.28 mg/dL; *P*<.01), and also the baseline GFR, which was significantly lower in the CO_2 group (60.86 ± 22.01 mL/min/1.73 m² vs 74.7 ± 23.62 mL/min/1.73 m²; *P*<.01), the other variables were not significantly

TABLE 1. Comparison of the participants' characteristics between the 2 study groups.

Characteristics	Iodine Contrast (n = 57)	Carbon Dioxide (n = 53)	*P*-Value
Female patients	11 (19.3%)	13 (24.5%)	.83
Age (years)	63.28 ± 11.74	62.50 ± 8.44	.69
Body mass index (kg/m²)	29.21 ± 2.29	29.86 ± 2.03	.10
Diabetes mellitus	23 (40.4%)	27 (50.7%)	.34
Dyslipidemia	15 (26.3%)	16 (30.2%)	.68
Cigarette smoking	36 (63.2%)	37 (69.8%)	.56
Ejection fraction (≤30%)	3 (5.3%)	1 (1.9%)	.62
Baseline glomerular filtration rate (mL/min)	74.7 ± 23.62	60.86 ± 22.01	<.01
Baseline creatinine (mg/dL)	1.13 ± 0.28	1.46 ± 0.45	<.01
Complaint at admission			.42
Claudication	41 (71.92%)	40 (75.47%)	
Critical limb ischemia	16 (28.08%)	13 (14.53%)	

Data presented as mean ± standard deviation or counts (percentages).

different between the 2 study groups. Diagnostic-only angiography was performed in 32 patients (29.0%) and diagnostic and endovascular procedures were performed in 78 patients (70.0%). Aortoiliac, femoropopliteal, and infrapopliteal endovascular procedures were performed in 15 (13.6%), 31 (28.1%), and 32 (29.0%) of the remaining population, respectively. All of the procedures were successful, without any major vascular or allergic contrast-medium related complications. In the CO_2 group, 12 patients (22.64%) experienced mild self-limiting lower-limb pain. The mean volume of the iodinated contrast medium was 11.35 ± 6.09 mL in the CO_2 group and 93.15± 43.01 mL in the ICA group.

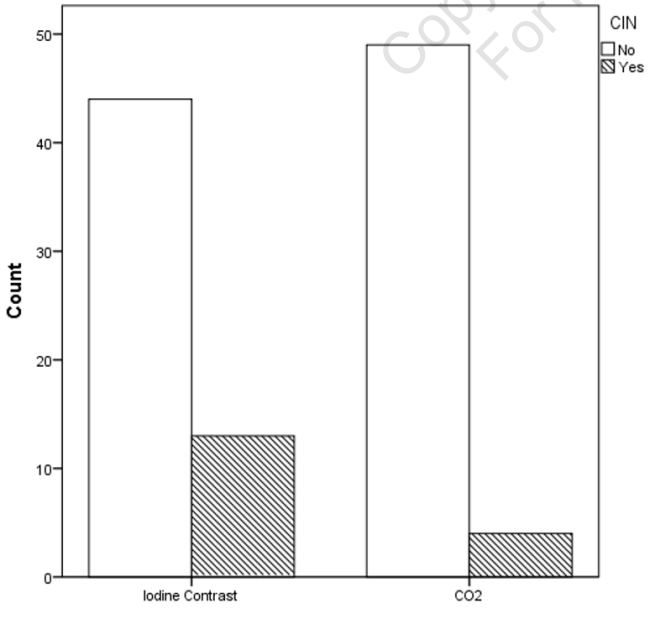

FIGURE 1. The bar chart depicts a comparison of the incidence of contrast-induced nephropathy (CIN) between the iodine contrast agent (ICA) group and the carbon dioxide (CO_2) group.

The incidence of CIN, as the primary endpoint, was higher in the ICA group than in the CO_2 group (13 [22.8%] vs 4 [7.5%]; *P*=.03) (**Figure 1**). The differences in terms of GFR and creatinine between the groups are summarized in **Table 2**. None of the patients in the 2 groups required hemodialysis. The incidence of CIN was correlated with a higher contrast volume. The mean ICA dose in patients without CIN was 44.54 ± 41.14 mL vs 100.88 ± 65.34 mL in those who developed CIN (*P*<.01). There were no deaths or need for renal replacement therapy during the 1-month follow-up, as the secondary endpoint.

The multivariate logistic regression model, after adjustments for the baseline creatinine level and other factors, showed that whereas no significant associations existed between CO_2 treatment and CIN incidence, there was a weak positive association between the volume of the iodinated contrast medium and CIN. The association between age and CIN, albeit non-significant, was considerable (**Figure 2**).

Discussion

To investigate the potential role of different confounding factors vis-à-vis CIN after invasive angiography, given the paucity of randomized controlled trials on the pathophysiology of CIN and the role of potential confounding factors such as catheter manipulation, we designed the present randomized controlled trial and assessed the effects of CO_2 in comparison with ICA in patients with mild-to-moderate renal impairment

Table 2. Creatinine and glomerular filtration rate alterations during the first 72 hours post procedure.

	Iodine Contrast	Carbon Dioxide	*P*-Value
Absolute creatinine change	0.0561	-0.1094	<.01
Perceptual/relative change (%)	7.5292	-6.5700	<.001
Absolute glomerular filtration rate change	-5.3018	4.6170	<.001
Perceptual/relative glomerular filtration rate change (%)	-3.5592	9.3129	<.001

undergoing lower-limb peripheral angiography. Our inclusion criteria ensured the presence of the fewest confounding factors. For instance, the study population consisted of patients with non-severe chronic kidney disease to lessen the role of renal dysfunction. Additionally, lower-limb angiography/angioplasty was chosen to omit the role of catheter manipulation higher than the renal arteries and the resultant distal embolization. Our results revealed a lower rate of CIN in the CO_2 group than in the ICA group (13 [22.8%] vs 4 [7.5%], respectively; *P*=.03). Importantly, the volume of the contrast medium compared with baseline GFR was an important predictor of CIN, even in a setting where the potential roles of catheter manipulation and microembolization were eliminated.[18] Although weak, this effect persisted after the multivariate analysis.

CIN is a generally uncommon but potentially devastating complication with significant morbidity and mortality.[19] In a previous study, CIN increased in-hospital mortality on average by 5.5-fold, with the rise persisting during a long-term follow-up.[4] Despite a significant rise in mortality in patients requiring dialysis, the impact of CIN on the population without the need for renal replacement therapy is also considerable. A previous investigation reported the occurrence of this rise in the mortality rate regardless of baseline creatinine.[20] Research has shown that the incidence of CIN varies according to patients'

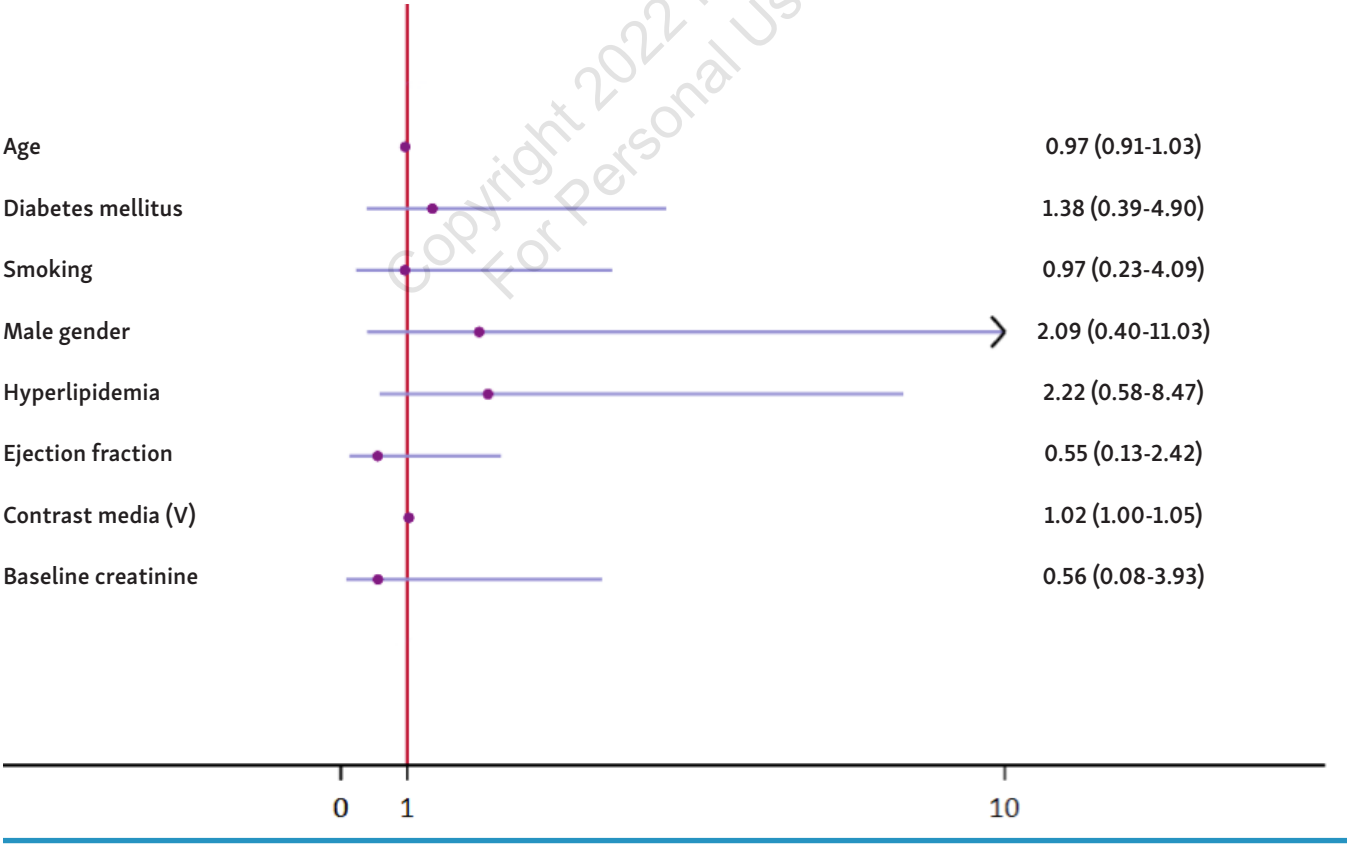

FIGURE 2. The image presents the results of the multivariate logistic regression model for adjusted associations between the study variables and the incidence of contrast-induced nephropathy. Data presented as odds ratio (95% confidence interval).

comorbidities and procedural settings,[3] but it persists as one of the most common etiologies of acquired in-hospital acute renal failure.[4] The average in-hospital and 1-year cost of CIN was reported to have increased by $10,345 and $11,812, respectively, which underscores the economic burden of the complication.[5] The results of a prior study showed that in patients complicated by CIN, compared with an uncomplicated population, hospital stay was lengthened irrespective of previous renal function (6.8 ± 7.1 days vs 2.3 ± 2.5 days in patients with previous kidney disease and 3.6 ± 5.1 days vs 1.8 ± 2.4 days in patients without kidney disease).[6] Patients suffering from peripheral artery disease and comorbidities, such as chronic kidney disease, diabetes mellitus, hypertension, and heart failure, as well as older age, are at a higher risk of CIN.[21,22] The roles of preventive measures such as hydration,[23] adjunctive therapies (eg, statin, N-acetylcysteine, and sodium bicarbonate),[24] and sophisticated methods like left ventricular end-diastolic pressure-guided hydration[25] are still controversial. The current medical armamentarium lacks a definitive treatment for this complication and the suggested preventive measures are controversial; hence, the significance of having a clear pathophysiological picture of CIN. The pathophysiology of CIN encompasses various factors, such as direct cytotoxic effects and the related acute sustained vasoconstriction, unstable hemodynamics, autocrine and paracrine factors, hypoxia, and direct tubular endothelial injury with reactive oxygen species.[26,27] Catheter manipulation and the ensuing microembolic showers through the kidney circulation are also deemed a potential cause of CIN.[12,14] Notably, chronic kidney disease (estimated GFR <60 mL/min/1.73 m^2) is regarded as an important predictor of CIN.[12,26]

There is a dearth of data in the existing literature on the mechanism of increased CIN incidence after intra-arterial ICA injection, especially in studies with a robust setting (ie, randomized controlled trials). Furthermore, due heed should be paid to microembolic showers on the distal vascular bed (including the renal arteries) following the manipulation of the descending aorta during catheterization. Therefore, we sought to assess the effects of the intra-arterial injection of the ICA in comparison with CO_2 on renal function and CIN incidence after endovascular procedures carried out below the origin of the renal arteries on the lower-limb vascular system. The benefits of CO_2 over ICA as the contrast medium for arteriography have been demonstrated in previous studies.[18,27,28] Nonetheless, the use and benefits of CO_2 as the routine contrast medium for peripheral and aortic arteriography constitute a new emerging topic.[24] No randomized studies have hitherto evaluated the effects of ICA compared with CO_2 on lower-limb angiographic procedures. Liss et al examined the role of CO_2 angiography in comparison with conventional angiography in patients who underwent renovascular intervention. Patients with a serum creatinine concentration of <200 mol/L (n = 82) were randomized prospectively to receive CO_2 with small added amounts of ioxaglaten (n = 37) or only ioxaglate (n = 45). The authors concluded that the amount of ICA significantly correlated with a higher risk of CIN (*P*=.01) and reported that the risk of CIN was higher among patients with a baseline GFR of <40 mL/min.[29] We showed a significantly higher rate of CIN in patients allocated to the ICA group vs the CO_2 group (13 [22.8%] vs 4 [7.5%], respectively; *P*=03).

In the current study, 7.5% of the patients assigned to CO_2 angiography were complicated by CIN, which is in accordance with the results of previous investigations, although the exact etiology of this observation has yet to be elucidated. Among the authors reporting a similar finding, Moos et al[30] reported a 0.5 mg/dL increase in the serum creatinine level and Fujihara et al[17] reported an incidence rate of 5.1% for CIN.

The recent advent of automated CO_2 injectors and improved image processing with the resulting better image quality have somewhat assuaged previous concerns regarding the probable incidence of CO_2 injection complications, such as explosive gas delivery and gas embolization.[26,31] In our study, except for mild self-limiting lower-limb and hypogastric pain, no CO_2-related complications occurred.

Study limitations. The results of the current investigation should be interpreted in light of the following limitations. First, the complete difference both in equipment for CO_2 and ICA injection and in imaging protocols concerning digital subtraction angiography precluded a blinded design. Second, despite our random assignment of the study population to CO_2 or ICA groups, the baseline creatinine level was higher in the CO_2 group. However, the final rate of CIN was significantly lower in the mentioned group, and importantly, baseline creatinine was not a significant predictor of the risk of CIN in our multivariate analysis. Third, we did not compare x-ray exposure time between our 2 study groups. Finally, our results would have been bolstered had we evaluated the long-term impact of CIN on patient survival and the related economic burden.

Conclusion

Patients with critical limb ischemia develop various comorbidities, which are likely to be increased by renal function aggravation. According to the results of the present study, CO_2 angiography was associated with a lower risk of CIN than ICA angiography in a patient cohort with mild-to-moderate renal dysfunction undergoing endovascular procedures. The ICA volume was still an important predictor of CIN in our patients with the lowest risk of microembolization due to catheter manipulation. Consequently, contrast-free angiography, even in patients with less severe forms of renal dysfunction, could be potentially beneficial, although larger investigations are required to confirm this strategy.

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Predictors of Long-Term Mortality in Patients Undergoing Major or Minor Lower-Extremity Amputations

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Abstract

Purpose. Amputation as the initial treatment of choice remains prevalent despite advances in revascularization techniques and medical therapy. We evaluated the 7-year mortality of patients undergoing major and minor lower-extremity amputations and determined the impact of risk factors on long-term mortality. **Methods.** Patients undergoing non-traumatic lower-extremity amputations from 2011 to 2017 were retrospectively studied at a single-center community hospital. Patients were divided into cohorts based on major or minor amputation. Kaplan-Meier analysis was used to assess long-term survival out to 7 years. Univariate and multivariate analyses identified predictors of long-term mortality. We further analyzed the incremental impact of multiple atherosclerotic risk factors on long-term mortality. **Results.** A total of 698 patients were included, of which 309 patients (44%) underwent major amputations and 389 (56%) underwent minor amputations. Patients with major amputations had 1-, 5-, and 7-year mortality of 20%, 53%, and 65%, respectively and patients with minor amputations had 1-, 5-, and 7-year mortality of 12%, 40%, and 51%, respectively ($P<.001$). Multivariate analysis demonstrated that coronary artery disease (CAD) (odds Ratio [OR], 3.25; $P<.001$), chronic kidney disease (CKD) (OR, 2.3; $P<.001$), and major amputations (OR, 1.5; $P=.02$) were predictors of long-term mortality. Coexistence of >2 atherosclerotic risk factors (hyperlipidemia, diabetes mellitus, CAD, and CKD) was associated with significant increase in long-term mortality. **Conclusion.** Long-term (7-year) mortality remains high after major and minor amputations in this contemporary dataset. Major amputation, CAD, and CKD are independent risk factors for long-term mortality. Coexistence of multiple atherosclerotic risk factors is associated with significantly high mortality and poor 7-year prognosis.

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Key words: amputation, atherosclerosis, critical limb ischemia, diabetic foot ulcer, mortality

As of 2005, there were approximately 1.6 million people living with amputations in the United States, with these numbers expected to double by 2050.[1] Vascular disease, traumatic accidents, and cancer are the 3 major reasons for amputations, with vascular disease accounting for the majority of cases. With the overall increasing age of the population and more patients suffering from multiple risk factors, such as diabetes mellitus (DM) and coronary artery disease (CAD), the incidence of lower-extremity amputation continues to rise as primary amputation, without revascularization, has remained the first-line therapy for a majority of the population.[1-8]

Major amputations result in increased mortality, risk of subsequent amputations, and inflated healthcare costs.[9] Current studies are limited by data from previous decades and the maximum long-term mortality previously reported is only out to 5 years. Multiple studies demonstrate mortality rates after major amputation ranging from 8%-20% at 30 days, 40%-50% at 1 year, and 77%-85% at 5 years.[8,10-12] Over the past decade, there has been significant improvement in revascularization therapies, wound care, and reinforcement from major vascular societies promoting limb salvage and establishment of multidisciplinary care teams.[13-18] It would be anticipated that implementation of these strategies would improve mortality rates after amputation. Yet, there remains a discordance in the dissemination of comprehensive, guideline-based vascular care and we do not know the overall impact of these recent advancements on long-term mortality.

In this study, we evaluated the following: (1) contemporary 7-year mortality among patients who underwent non-traumatic major and minor amputations in a rural community hospital; (2) predictors of long-term mortality; and (3) aggregate impact of multiple atherosclerotic risk factors on long-term mortality.

Methods

Patients. This retrospective chart review was conducted at a rural community hospital and comprised patients who received a lower-extremity amputation in the contemporary era from 2011 to 2017. Patients were identified using the Internal Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10 codes for lower-extremity amputations (**Appendix 1** and **Appendix 2**). All traumatic and cancer-related amputations were excluded. Patients undergoing amputations secondary to acute limb ischemia, critical limb ischemia (CLI), and diabetic foot ulcer were included in the study. Institutional review board approval was obtained from the Western Institutional Review Board and the requirement for informed consent was waived as no patients were contacted for this study.

Amputations. Patients were divided into cohorts based on the level of amputation (major or minor). *Major amputation* was defined as transection occurring proximal to the tarsometatarsal joint, which included transtibial, below-the-knee, and above-the-knee amputations. *Minor amputation* was defined as transection occurring distal to the tarsometatarsal joint, which included toe(s), transmetatarsal, Chopart, and Lisfranc amputations.

Any first major amputation (even if the patient received a prior minor amputation during the study) that occurred during the study period was included in the major amputation cohort. Any subsequent major or minor amputation(s) on the same patient were excluded from analysis. In patients who had only minor amputation(s), the first minor amputation was included in the minor amputation cohort. Any subsequent amputation(s) on the same patient were excluded. *Primary amputation* is defined as any amputation occurring without either surgical or endovascular revascularization intervention occurring within the year leading up to amputation.

Baseline demographics. Charts were reviewed for age, gender, race/ethnicity, and the presence of risk factors, including hypertension, hyperlipidemia (HLD), DM, chronic kidney disease (CKD; defined as glomerular filtration rate ≤60 mL/min/1.73 m^2), CAD, peripheral artery disease, and obesity (body mass index >30 kg/m^2) documented in the history. Smoking was considered present if the patient was either a current or former smoker. History of prior amputation, presence of a wound, and clinical diagnosis of osteomyelitis or gangrene prior to amputation were also collected.

In-hospital outcomes. The in-hospital outcomes that were assessed included length of stay, discharge destination (either home or skilled nursing facility/rehabilitation facility), and in-hospital mortality.

Long-term mortality. Long-term mortality was collected from 2011 to 2017 and included the early release data from 2018 using the United States National Death Index. The National Death Index is a centralized database of death record information on file in the state vital statistics offices established by the National Center for Health Statistics.[19] Detailed records including patient's name, date of birth, social security number, age, gender, race, marital status, and state of residence were submitted, as available. Each patient who received matching records within the database was reviewed in detail to validate mortality based on the number of matching components within the records.

Patient risk factors. The risk factors HLD, DM, CAD, and CKD were chosen to analyze for mortality since they have been identified as atherosclerotic risk factors for poor outcomes and mortality in patients with peripheral arterial disease. Hypertension was not analyzed since it was present in nearly 90% of this patient population and previous CLI studies/models have shown that other comorbidities better explain adverse events and mortality rates seen in patients with peripheral arterial disease and CLI. All patients were classified into 4 groups based on the cumulative number of the chosen risk factors present. To assess the long-term mortality, Kaplan-Meier survival curve analysis was performed based on the coexistence of 1, 2, 3, and 4 risk factors.

Statistical analysis. XLSTAT, version 2019.3.2 (XLSTAT-LifeScience Data Analysis and Statistical Solutions) was used for data collection and statistical analysis. Values presented are number (%) or mean ± standard deviation. Kaplan-Meier analysis (confidence interval [CI] determined via the Greenwood method and log-rank test statistic for comparison of survival functions/curves) was used to estimate freedom from death. For multiple comparisons, the adjusted *P*-values were generated via the Dunn-Sidak statistical method. In addition, logistic-regression multivariable analyses for predictors of death were conducted on all subjects. Briefly, a forward stepwise model selection was utilized with a likelihood ratio criterion and a probability for entry and removal in the multivariable model of 0.1 and 0.2, respectively. The overall classic logistic model was set to a tolerance of 0.001, CI of 95%, stop conditions of 100 iterations, a convergence of 0.000001, and a constraint of a 1=0. Variables included in a univariable model were age, race/ethnicity, obesity, smoking, CKD, DM, HLD, CAD, gangrene, prior amputation, and major amputation. Of the variables included in the univariable model, CAD, CKD, DM, age, prior amputation, and major amputation met the criterion (as described above) for inclusion in the multivariable model. To assess the trends in mortality between major and minor

TABLE 1. Baseline demographics and clinical characteristics.

Characteristics	Major Amputation (n = 309)	Minor Amputation (n = 389)	*P*-Value
Age (years)	62.7 ± 13.7	63.3 ± 14.2	.72
Male gender	209 (67.6%)	261 (67.1%)	.88
Race/ethnicity			.42
Caucasian	216 (69.9%)	275 (70.7%)	
Black	20 (6.5%)	16 (4.1%)	
Asian	2 (0.6%)	1 (0.3%)	
Hispanic	71 (23.0%)	97 (24.9%)	
Obese (body mass index >30 kg/m^2)	142 (46.0%)	168 (43.2%)	.46
Peripheral artery disease	141 (45.6%)	167 (42.9%)	.48
Smoker	155 (50.2%)	195 (50.1%)	.99
Chronic kidney disease	107 (34.6%)	116 (29.8%)	.18
Diabetes mellitus	215 (69.6%)	304 (78.1%)	.01
Hyperlipidemia	210 (68.0%)	252 (64.8%)	.38
Hypertension	270 (87.4%)	344 (88.4%)	.67
Coronary artery disease	139 (45.0%)	149 (38.3%)	.08
Gangrene	140 (45.3%)	179 (46.0%)	.93
History of prior amputation	76 (24.6%)	93 (23.9%)	.83
Wound	294 (95.1%)	366 (94.1%)	.54
Osteomyelitis	118 (38.2%)	142 (36.5%)	.80

Data presented as count (%) or mean ± standard deviation.
P-values for quantitative variables are from the Mann-Whitney U test. *P*-values for qualitative variables are from the Chi-square test or the Fisher's exact test (if theoretical frequencies were <5).

amputations, Mann-Kendall test was performed. The threshold of statistical significance was *P*<.05.

Results

A total of 698 patients were identified as having undergone non-traumatic lower-extremity amputation(s) during the study period. Major amputations were performed in 309 patients (44%) and minor amputations were performed in 389 patients (56%).

Baseline characteristics. Baseline characteristics of the 2 cohorts are described in **Table 1**. The average age was 62.7 ± 13.7 years in the major amputation group and 63.3 ± 14.2 years in the minor amputation group (*P*=.72). There was no statistical difference between any of the baseline characteristics, except patients who underwent minor amputations had a higher prevalence of DM (78%) compared with patients who underwent major amputations (70%; *P*=.01). There was no statistically significant difference in clinical presentation between major and minor amputations: wound (95% vs 94%, respectively; *P*=.54), gangrene (45% vs 46%, respectively; *P*=.93), and clinical osteomyelitis (38% vs 36%, respectively; *P*= .80).

In-hospital outcomes. The length of stay was significantly higher in patients who underwent major amputations (12.1 days) compared with minor amputations (10.1 days; *P*<.001) (**Table 2**). A majority of the major amputation patients were discharged to a skilled nursing facility (61%) and 37% of the patients were discharged to home (*P*<.001). A majority of the minor amputation patients were discharged home (72%), with 28% discharged to a skilled nursing/rehabilitation facility (*P*<.001). There was a numerically higher trend for in-hospital mortality among patients who underwent major amputations, although it did not reach statistical significance (*P*=.05).

Long-term mortality. The 7-year mortality rates for patients undergoing major or minor amputations are demonstrated in the bar graph and Kaplan-Meier analysis (**Figure 1** and **Figure 2**). The mean survival time was significantly higher for patients undergoing minor amputations (5.4 years) vs major amputations

TABLE 2. In-hospital outcomes.

	Major Amputation (n = 309)	Minor Amputation (n = 389)	*P*-Value
Length of Stay (days)	12.1 ± 8.8	10.1 ± 8.9	<.001
Discharge destination			<.001
Home	115 (37.2%)	280 (72.0%)	<.001
Skilled nurse facility/ rehabilitation	189 (61.2%)	108 (27.8%)	<.001
In-hospital mortality	5 (1.6%)	1 (0.3%)	.05

Data presented as count (%) or mean ± standard deviation.
P-values for quantitative variables are from the Mann-Whitney U test. *P*-values for qualitative variables are from the Chi-square test or the Fisher's exact test (if theoretical frequencies were <5).

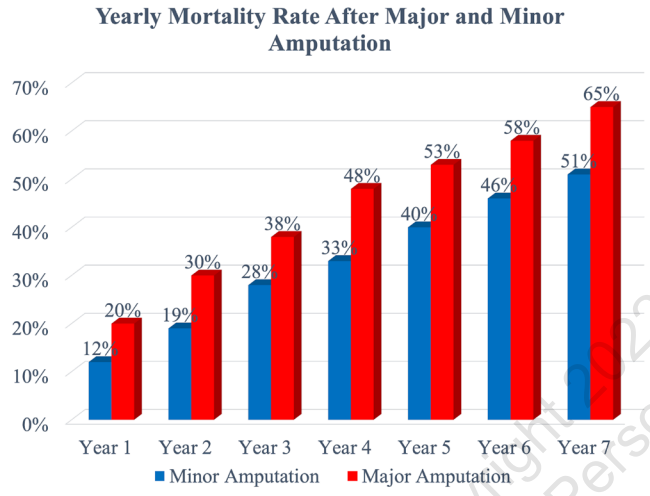
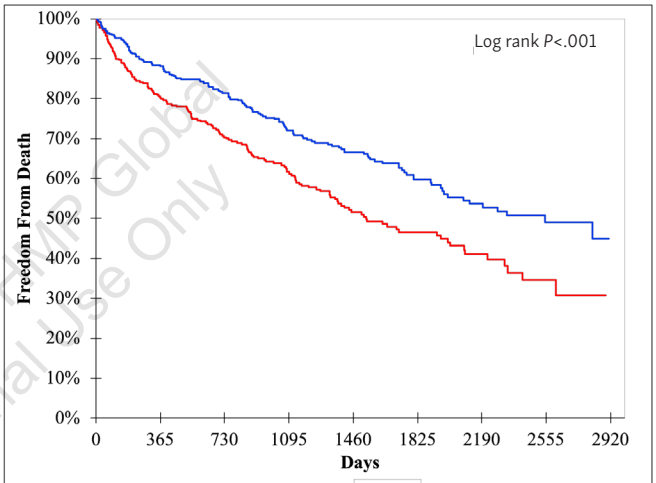


FIGURE 1. Bar graph demonstrating the yearly mortality rates of patients with major and minor amputations for 7 years.



Years	0	1	2	3	4	5	6	7	8
Days	0	365	730	1095	1460	1825	2190	2555	2920
(1) Major AMP									
At risk	309	248	193	146	95	62	43	12	1
Events	0	61	90	112	133	141	146	151	152
FF Death ± SE (%)	100 ± 0.0	80.2 ± 2.3	70.3 ± 2.6	61.6 ± 2.9	51.6 ± 3.2	46.6 ± 3.3	42.1 ± 3.6	34.5 ± 4.3	30.7 ± 5.3
Mean survival time	1617 days (4.4 years)								
(2) Minor AMP									
At risk	389	342	273	198	156	97	61	28	1
Events	0	46	71	99	113	126	134	138	139
FF Death ± SE (%)	100 ± 0.00	88.1 ± 1.6	81.3 ± 2.0	72.0 ± 2.4	66.5 ± 2.7	59.7 ± 3.0	53.6 ± 3.4	49.0 ± 3.8	44.9 ± 5.3
Mean survival time	1972 days (5.4 years)								

FIGURE 2. Kaplan-Meier survival analysis over 7 years from the date of first major or minor amputation.

(4.4 years). The mortality rates for patients at 1, 5, and 7 years were 20%, 53%, and 65% for major amputations and 12%, 40%, and 51%, respectively, for minor amputations (log rank *P*<.001).

When the mortality trends were analyzed, there was significant difference in mortality trends from year 0 to year 7 (*P*=.046). There was significant difference in mortality between major and minor amputations in year 0-year 1 (*P*<.01). When the analysis was performed excluding the first year, ie, year 1 to year 7, the trend analysis did not reach clinical significance (*P*=.17).

Predictors of long-term mortality. A multivariate analysis was conducted to identify independent variables associated with increased mortality. Variables that reached statistical significance are summarized in **Table 3**. This demonstrated that patients with a history of CAD had 3.3 times higher odds (*P*<.001), history of CKD had 2.3 times higher odds (*P*<.001), and patients undergoing major amputations had 1.5 times higher odds of long-term mortality (*P*=.02). Patients with history of DM were found to have protective impact on long-term mortality (odds ratio, 0.64; *P*=.02).

Long-term mortality with individual risk factors. Four major atherosclerotic risk factors (HLD, DM, CAD, and CKD) were analyzed individually for long-term survival in all patients (**Figure 3**). Patients with a single risk factor of HLD, CAD, or CKD demonstrated increased mortality after any amputation. DM did not have any impact on mortality after amputation.

TABLE 3. Multivariate analysis of predictors of long-term mortality for all patients.

	All Amputation Patients (n = 698)	
	Odds Ratio (95% CI)	*P*-Value
Coronary artery disease	3.255 (2.221-4.772)	<.001
Chronic kidney disease	2.327 (1.640-3.303)	<.001
Major lower-extremity amputation	1.511 (1.083-2.109)	.02

Significant predictors shown. CI = confidence interval.

Long-term mortality for cumulative risk factors. There was not a significant difference between the presence of 1 risk factor vs 2 (*P*=.68) (**Figure 4**). Patients with 3 or 4 aggregate risk factors demonstrated increased mortality at 1, 5, and 7 years (3 risk factors: 17%, 53%, and 74%; 4 risk factors : 31%, 74%, and 83%, respectively).

Discussion

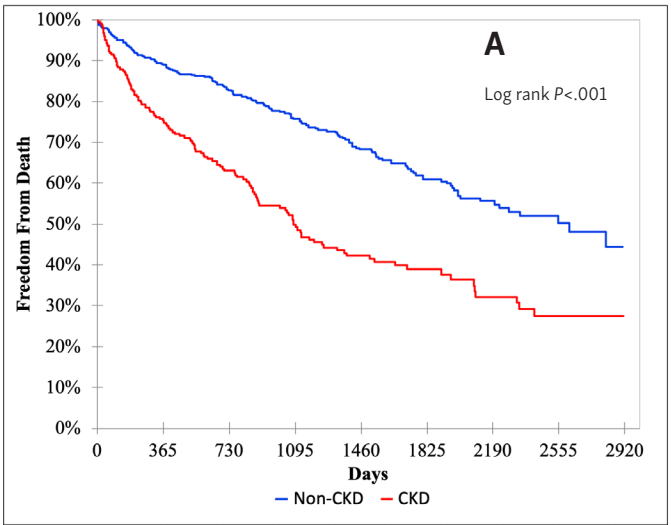
The main results of this study were: (1) patients undergoing major amputations had longer length of stay and were more frequently discharged to a skilled nursing facility or rehabilitation as opposed to discharged to home; (2) major amputation is associated with higher 7-year mortality compared with minor amputation, and this appears driven by differences in the first year; (3) in order of hazard, CAD, CKD, and major amputation were independent predictors of mortality for patients undergoing amputations; and (4)coexistence of >2 atherosclerotic risk factors was associated with a substantial increase in 7-year mortality.

CLI and subsequent major amputations carry a 5-year mortality rate of 60% in previous studies.[20] These mortality rates are higher than 5-year mortality rates of ovarian cancer (53%), myeloma (50%), leukemia (39%), colorectal cancer (35%), and breast cancer (10%), prompting recent interest in multidisciplinary care, early revascularization, and high adherence to guideline-directed medical treatment.[21] Our study evaluated the 7-year mortality of patients undergoing major and minor amputations in a contemporary dataset. It is promising that in our population, the 5-year mortality was 40% for minor amputations and 53% for major amputations. Even though the mortality rate is lower than previous reports, direct comparison is difficult considering the heterogeneity of the population and the inclusion of both major and minor amputations. In our study, we report a 7-year mortality of 65% for patients undergoing major amputations and 51% for patients undergoing minor amputations, indicating a continual increase in mortality up to 7 years.

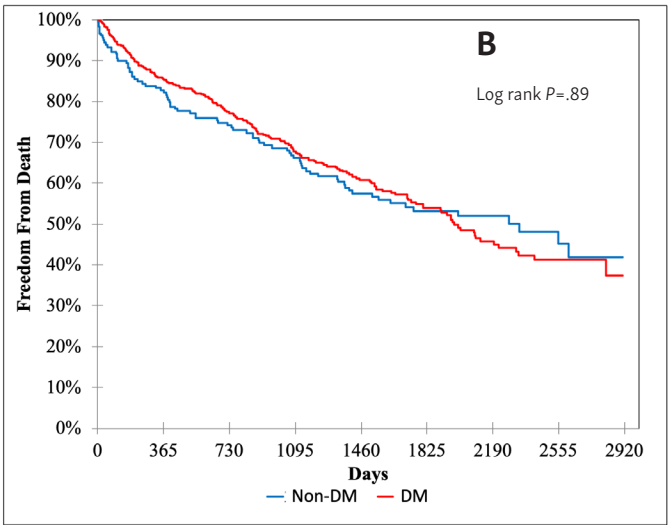
Minor amputations have a lower in-hospital mortality and improved outcomes compared with patients undergoing major amputations.[22] However, there are limited data on whether the short-term mortality benefits of minor amputations persist on long-term follow-up. This study demonstrated the mortality advantage for patients undergoing minor amputations persisted out to 7 years, although this remains driven by differences in the first year. We also found that major amputation was an independent predictor of mortality in this study. In landmark analysis after one year, there was no difference in trends for mortality between major and minor amputations. It is likely that the higher surgical risk of a major amputation on the cardiovascular system, impaired mobility, longer length of stay, and more frequent discharge to long-term care facilities contributed to early mortality.

The clinical relevance of this finding is that the avoidance of major amputation itself may impact the 1-year and hence long-term mortality of CLI patients. Regardless of revascularization strategy, whether endovascular or surgical, it is likely that a subset of major amputations may be converted to minor amputation or delayed amputation, potentially improving early and long-term mortality.[23-25] Conservative management of lower-extremity non-healing wounds would not increase mortality in selected patients and has been reported previously.[26] We also found that major amputation patients had higher likelihood of being discharged to a skilled nursing/rehabilitation facility rather than being discharged home, which causes an increased burden upon the healthcare system and potential for nosocomial infection.[9,27] From these observations in the literature, it is reasonable to assume that prompt and complete revascularization with the intention of conversion of major amputation to a minor amputation (or deferred amputation) improves mobility and independence, allows patients to return home, and may improve quality of life, healthcare costs, length of stay, and long-term mortality, although further data in this space would be required.

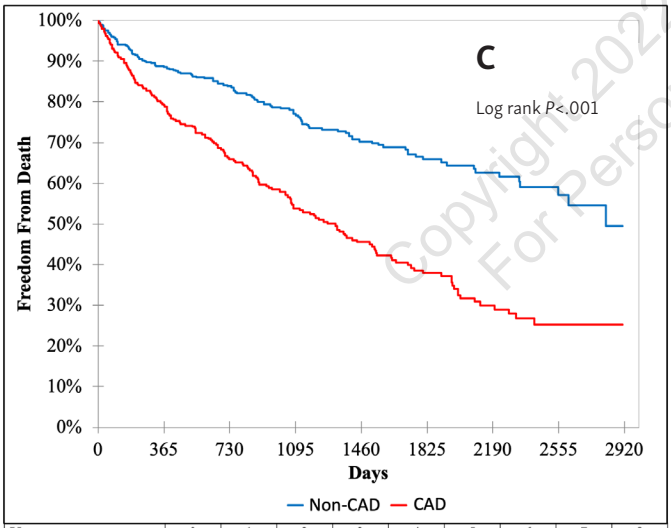
The long-term mortality for patients undergoing any amputation gradually increased beyond 1 year. This could be due to associated risk factors. In a multivariate analysis, we confirmed that the atherosclerotic risk factors of CAD and CKD are independent predictors for long-term mortality, which has been validated in multiple studies.[28-30] The coexistence of 1 or 2 atherosclerotic risk factors did not significantly increase mortality; however, coexistence of 3 and 4 risk factors reduced the survival by an average of 1.2 years. Interestingly, the presence of DM tracked with lower mortality. However, as the prevalence of DM was higher among patients with minor amputations, it is possible that this association confounded the potential impact of this known risk factor. Clinically, this information may help with risk stratification for patients with multiple atherosclerotic risk factors when discussing long-term prognosis. Optimal treatment of atherosclerotic risk factors, aggressive medical therapy, smoking cessation, and exercise are likely as important as performing timely revascularization in determining long-term mortality. Multiple studies have also shown that statin therapy can reduce mortality in patients



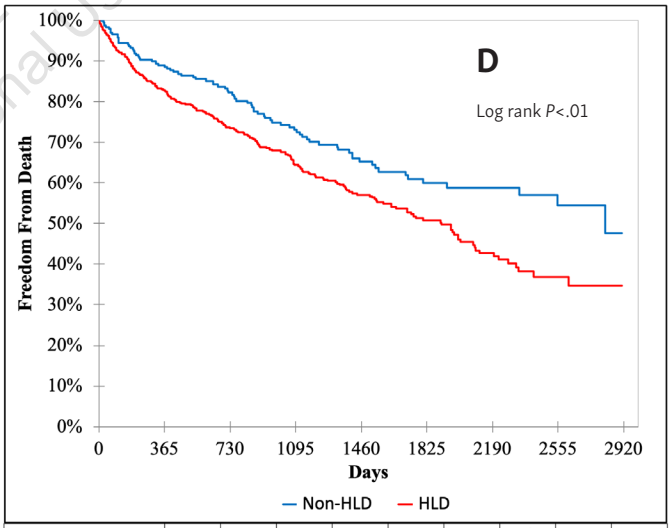
Years	0	1	2	3	4	5	6	7	8
Days	0	365	730	1095	1460	1825	2190	2555	2920
CKD									
At risk	223	167	129	83	58	38	24	11	1
Events	0	55	81	105	117	121	126	129	129
FF Death ± SE (%)	100 ± 0.0	75.3 ± 2.9	63.0 ± 3.3	49.8 ± 3.5	42.2 ± 3.6	38.9 ± 3.7	32.1 ± 4.1	27.4 ± 4.3	27.4 ± 4.3
Mean survival time	1414 days (3.9 years)								
Non-CKD									
At risk	475	423	338	260	193	121	69	29	1
Events	0	52	80	106	129	146	155	160	162
FF Death ± SE (%)	100 ± 0.00	89.0 ± 1.4	82.7 ± 1.8	75.7 ± 2.1	68.3 ± 2.4	61.0 ± 2.7	55.6 ± 3.0	50.3 ± 3.6	44.4 ± 5.2
Mean survival time	2013 days (5.5 years)								



Years	0	1	2	3	4	5	6	7	8
Days	0	365	730	1095	1460	1825	2190	2555	2920
DM									
At risk	519	442	344	236	171	105	60	24	1
Events	0	75	115	152	174	190	203	208	209
FF Death ± SE (%)	100 ± 0.0	85.5 ± 1.5	77.2 ± 1.9	67.7 ± 2.2	60.7 ± 2.4	53.9 ± 2.7	45.8 ± 3.1	41.2 ± 3.4	37.5 ± 4.7
Mean survival time	1814 days (5.0 years)								
Non-DM									
At risk	179	148	123	107	80	54	33	16	1
Events	0	32	46	59	72	77	78	81	82
FF Death ± SE (%)	100 ± 0.00	82.1 ± 2.9	74.1 ± 3.3	66.1 ± 3.6	57.5 ± 3.9	53.2 ± 4.0	52.0 ± 4.1	45.2 ± 5.2	42.0 ± 5.7
Mean survival time	1802 days (4.9 years)								

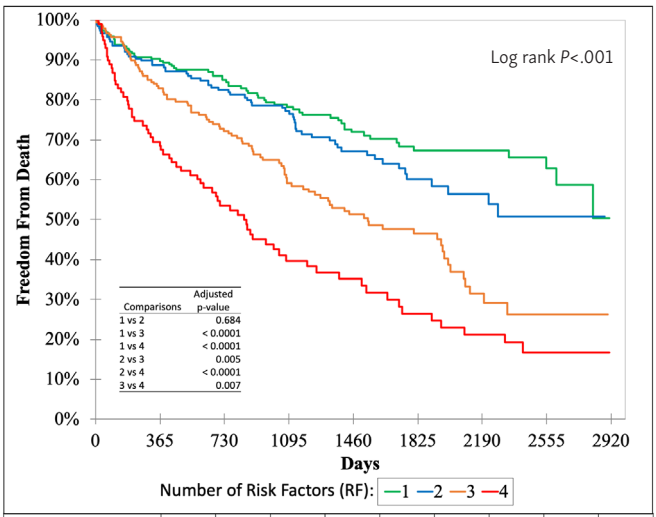


Years	0	1	2	3	4	5	6	7	8
Days	0	365	730	1095	1460	1825	2190	2555	2920
CAD									
At risk	288	227	171	117	87	56	31	13	1
Events	0	60	96	124	141	154	164	168	168
FF Death ± SE (%)	100 ± 0.0	79.1 ± 2.4	66.0 ± 2.8	53.8 ± 3.1	45.5 ± 3.2	37.9 ± 3.3	30.0 ± 3.4	25.3 ± 3.6	25.3 ± 3.6
Mean survival time	1445 days (4.0 years)								
Non-CAD									
At risk	410	363	295	226	164	103	62	27	1
Events	0	47	65	87	105	113	117	121	123
FF Death ± SE (%)	100 ± 0.00	88.5 ± 1.6	83.8 ± 1.8	77.0 ± 2.2	70.3 ± 2.5	65.9 ± 2.8	62.6 ± 3.1	57.1 ± 3.9	49.6 ± 6.3
Mean survival time	2104 days (5.8 years)								



Years	0	1	2	3	4	5	6	7	8
Days	0	365	730	1095	1460	1825	2190	2555	2920
HLD									
At risk	462	380	298	217	163	100	55	20	1
Events	0	80	120	153	176	191	204	210	211
FF Death ± SE (%)	100 ± 0.0	82.6 ± 1.8	73.5 ± 2.1	64.4 ± 2.4	57.1 ± 2.5	50.8 ± 2.7	42.7 ± 3.1	36.9 ± 3.5	34.6 ± 4.0
Mean survival time	1711 days (4.7 years)								
Non-HLD									
At risk	236	210	168	126	88	59	38	20	1
Events	0	27	41	58	70	76	77	79	80
FF Death ± SE (%)	100 ± 0.00	88.6 ± 2.1	82.2 ± 2.5	73.1 ± 3.1	65.2 ± 3.5	59.9 ± 3.8	58.7 ± 3.9	54.5 ± 4.7	47.7 ± 7.6
Mean survival time	2022 days (5.5 years)								

FIGURE 3. Kaplan-Meier survival analysis for the presence of different risk factors: (A) chronic kidney disease (CKD); (B) diabetes mellitus (DM); (C) coronary artery disease (CAD); and (D) hyperlipidemia (HLD). FF = freedom from; SE = standard error.



Years	0	1	2	3	4	5	6	7	8
Days	0	365	730	1095	1460	1825	2190	2555	2920
RF1									
At risk	225	203	163	128	95	67	44	21	1
Events	0	23	33	45	54	59	59	61	63
FF Death ± SE (%)	100 ± 0.0	89.8 ± 2.0	85.0 ± 2.4	78.2 ± 2.9	71.9 ± 3.4	67.4 ± 3.7	67.4 ± 3.7	62.8 ± 4.7	50.4 ± 9.2
Mean survival time	2169 days (5.9 years)								
RF2									
At risk	187	166	135	107	75	41	23	10	1
Events	0	21	32	40	53	59	61	63	63
FF Death ± SE (%)	100 ± 0.00	88.7 ± 2.3	82.5 ± 2.8	77.2 ± 3.2	67.2 ± 3.8	60.1 ± 4.4	56.4 ± 4.8	50.8 ± 5.8	50.8 ± 5.8
Mean survival time	1990 days (5.5 years)								
RF3									
At risk	187	156	121	82	62	37	15	6	1
Events	0	32	51	70	80	85	94	96	96
FF Death ± SE (%)	100 ± 0.00	82.9 ± 2.8	72.2 ± 3.3	59.1 ± 3.9	51.3 ± 4.1	46.5 ± 4.2	31.4 ± 5.1	26.2 ± 5.4	26.2 ± 5.4
Mean survival time	1572 days (4.3 years)								
RF4									
At risk	99	67	49	28	21	16	13	5	1
Events	0	31	45	56	59	64	67	69	69
FF Death ± SE (%)	100 ± 0.00	68.5 ± 4.7	53.5 ± 5.1	39.7 ± 5.2	35.2 ± 5.3	26.4 ± 5.2	21.1 ± 5.0	16.8 ± 4.8	16.8 ± 4.8
Mean survival time	1140 days (3.1 years)								

FIGURE 4. Kaplan-Meier survival analysis over 7 years following first major or minor amputation for cumulative risk factors. FF = freedom from; RF = risk factor; SE = standard error.

with peripheral arterial disease and those undergoing amputations.[31,32] As far as we know, this is the first study demonstrating the incremental effect of multiple atherosclerotic risk factors on long-term mortality for patients undergoing amputations, validating the current drive toward CLI teams with aggressive, multi-disciplinary care. In addition, the more than 3-fold increased odds of mortality among patients with CAD suggests aggressive surveillance and management of this risk factor in particular is paramount.

Study limitations. There are inherent limitations given the retrospective nature of this study. However, a randomized controlled trial is unlikely as revascularization therapies are proven to be beneficial compared with primary amputation, and the decision to perform major vs minor amputation is clinically driven. The medical therapy and revascularization strategies were not reported in this study, and therefore we cannot account for differences in pharmacologic or endovascular treatment leading up to or in the years following amputation. Mortality information was obtained from the National Death Index. Although administrative databases are prone to errors, patient-level data collected from our institution and multiple patient identifiers submitted could decrease potential bias. Other confounding variables, such as (but not limited to) congestive heart failure, dementia/delirium, and ambulatory status, which were not reported in this study, could have impact on the long-term mortality. The quality of life after amputations as long-term health outcome was not reported in this study.

Conclusion

This is the first study demonstrating long-term, 7-year mortality in a contemporary population undergoing major and minor amputations in the United States. Mortality is highest in the first year, with a trend of higher mortality in patients undergoing major amputation, and continues to increase over time. Logistic multivariable analysis indicated that CAD, CKD, and major amputation are predictors of long-term mortality in this patient population. The coexistence of 3 or more atherosclerotic risk factors is associated with a significant incremental increase on long-term mortality. Further studies are needed to see whether multidisciplinary teams prioritizing early complete revascularization will improve outcomes in this complex patient population.

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Supplemental Materials

APPENDIX 1. ICD-9 procedural coding to identify patients with lower-extremity amputations between 2011-2017.

ICD-9 Procedural Codes	Description
84.17	Above the knee -Amputation of leg through femur -Amputation of thigh -Conversion of below-knee amputation to above-knee amputation -Supracondylar above-knee amputation
84.15	Below the knee -Amputation of leg through tibia and fibula
84.16	Disarticulation of knee -Batch, Spitler, and McFadden amputation -Mazet amputation -S.P. Rogers amputation
84.12	Amputation through foot -Amputation of forefoot -Amputation through middle of foot -Chopart's amputation -Midtarsal amputation -Transmetatarsal amputation
84.11	Amputation of toe -Amputation through metatarsophalangeal joint -Disarticulation of toe -Metatarsal head amputation -Ray amputation of foot

APPENDIX 2. ICD-10 procedural coding to identify patients with lower-extremity amputations between 2011-2017.

ICD-10 Procedural Codes	Description
Above the knee	
0Y6D0Z1	Detachment at left upper leg, high, open approach
0Y6C0Z1	Detachment at right upper leg, high, open approach
0Y6D0Z2	Detachment at left upper leg, mid, open approach
0Y6C0Z2	Detachment at right upper leg, mid, open approach
0Y6D0Z3	Detachment at left upper leg, low, open approach
0Y6C0Z3	Detachment at right upper leg, low, open approach
Below the knee	
0Y6J0Z1	Detachment at left lower leg, high, open approach
0Y6H0Z1	Detachment at right lower leg, high, open approach
0Y6J0Z2	Detachment at left lower leg, mid, open approach
0Y6H0Z2	Detachment at right lower leg, mid, open approach
0Y6J0Z3	Detachment at left lower leg, low, open approach
0Y6H0Z3	Detachment at right lower leg, low, open approach
Foot (complete) (Chopart, Lisfranc, disarticulation through the ankle, transmetatarsal)	
0Y6N0Z0	Detachment at left foot, complete, open approach
0Y6M0Z0	Detachment at right foot, complete, open approach
Foot (partial) (metatarsal shaft, transmetatarsal, metatarsal level)	
0Y6N0Z9	Detachment at left foot, partial 1st ray, open ppproach
0Y6N0ZB	Detachment at left foot, partial 2nd ray, open ppproach
0Y6N0ZC	Detachment at left foot, partial 3rd ray, open ppproach
0Y6N0ZD	Detachment at left foot, partial 4th ray, open ppproach
0Y6N0ZF	Detachment at left foot, partial 5th ray, open ppproach
0Y6M0Z9	Detachment at right foot, partial 1st ray, open ppproach
0Y6M0ZB	Detachment at right foot, partial 2nd ray, open ppproach
0Y6M0ZC	Detachment at right foot, partial 3rd ray, open ppproach
0Y6M0ZD	Detachment at right foot, partial 4th ray, open ppproach
0Y6M0ZF	Detachment at right foot, partial 5th ray, open ppproach
Toes	
0Y6N0Z4	Detachment at left foot, partial 1st ray, open ppproach
0Y6M0Z4	Detachment at left foot, partial 2nd ray, open ppproach
0Y6N0Z5	Detachment at left foot, partial 3rd ray, open ppproach
0Y6M0Z5	Detachment at left foot, partial 4th ray, open ppproach
0Y6N0Z6	Detachment at left foot, partial 5th ray, open ppproach
0Y6M0Z6	Detachment at right foot, partial 1st ray, open ppproach
0Y6N0Z7	Detachment at right foot, partial 2nd ray, open ppproach
0Y6M0Z7	Detachment at right foot, partial 3rd ray, open ppproach
0Y6N0Z8	Detachment at right foot, partial 4th ray, open ppproach
0Y6M0Z8	Detachment at right foot, partial 5th ray, open ppproach

Review

Orbital Atherectomy Treatment of Peripheral Artery Disease and Critical Limb Ischemia

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Abstract

Orbital atherectomy (OA), a unique form of atherectomy, utilizes orbital sanding and pulsatile forces to deliver effective treatment of peripheral atherosclerotic lesions with varying levels of occlusion and calcification. This approach to endovascular therapy involves the use of differential sanding to preferentially ablate fibrous, fibrofatty and calcified lesions, while deflecting healthy tissue away from the crown. The eccentrically mounted crown design also allows the device to generate pulsatile forces that may penetrate the medial layer and fracture calcium, resulting in compliance change that facilitates low pressure balloon angioplasty and reduces the need for bailout stenting. The combination of plaque modification, improved vessel compliance, and lumen enlargement via OA can effectively restore blood flow in vessels above- and below-the-knee, relieving symptoms and improving limb salvage rates in patients with peripheral artery disease (PAD) and critical limb ischemia (CLI). Numerous peripheral OA clinical studies have confirmed the high rates of procedural success, freedom-from (FF) major adverse events, and FF major amputation. In addition, economic analyses have also shown the value of OA as a first line endovascular therapy for PAD and CLI. We review here the mechanism of action of OA, supporting clinical study evidence, and corresponding economic analyses.

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Key words: orbital atherectomy; peripheral artery disease; critical limb ischemia

Peripheral artery disease (PAD) is becoming extremely common worldwide, especially as risk factors and independent predictors for PAD rise to pandemic proportions. PAD affects more than 202 million people worldwide, and is prevalent in both high and low income countries.[1] Approximately 18 million Americans have PAD and 2 million of these patients suffer from critical limb ischemia (CLI),[2,3] the end stage of PAD.[4] CLI is highly prevalent in older patients with diabetes and/or end-stage renal disease[5] and is associated with high risk of amputation and mortality.[6] As shown in **Figure 1**, the results following lower extremity amputation can be devastating — 27% of these patients will have one or more re-amputation(s) within 1 year,[7] 35% will have a higher level of limb loss,[8] and 55% will have a contralateral limb amputation within 2-3 years.[9] Furthermore, the mortality rates after primary amputation are very high, with rates ranging from 9% to 33% at 1 year[7,8,10,11] and 26% to 82% at 5 years.[7,10–12] Despite such devastating outcomes, primary amputation remains a common treatment modality for CLI.[13]

The most severe forms of PAD and CLI often involve heavily calcified lesions which may be more difficult to treat with angioplasty alone. One of the main risk factors for atherosclerotic plaque and vascular calcification is advanced age, since atherosclerotic lesions and calcium increase throughout life.[14] Other risk factors include hypercholesterolemia, diabetes, hypertension, and smoking, many of which are on the rise worldwide.[1,15] Historical methods of intervention, including balloon angioplasty, may be less effective for treating calcified lesions. These challenging lesions require higher inflation pressure, thus increasing the incidence of plaque rupture, embolization, and dissection.[16] Orbital atherectomy (OA; Cardiovascular Systems, Inc.) is a unique device with an eccentrically mounted crown that treats peripheral lesions above-the-knee (ATK) and below-the-knee (BTK) via a dual mechanism of action (MOA): orbital sanding and pulsatile (repeated striking) forces. The orbital sanding removes intimal plaque while the repeated impact of the crown on the vessel wall (pulsatile forces) may fracture

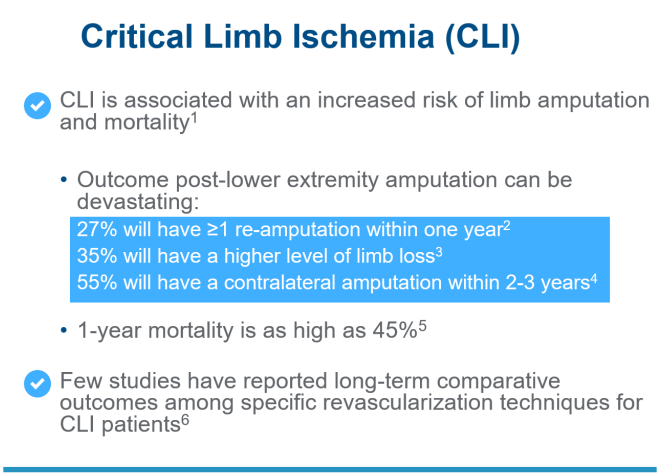

FIGURE 1. [1]Levin SR, et al. *Trends Cardiovasc Med.* 2019;S1050-1738(19)30047-7. [2]Jindeel A, Narahara K. *Int J Low Extrem Wounds.* 2012;11(3):177-179. [3]Dillingham TR, et al. *Arch Phys Med Rehabil.* 2005;86(3):480-486. [4]Pasquina PF, et al. *Curr Phys Med Rehabil Rep.* 2014;2(4):273-289. [5]Mustapha J, et al. *J Endovasc Ther.* 2019;26(2):143–154. [6]Mustapha J, et al. *Circ Cardiovasc Interv.* 2019;12(9):e008097.

medial calcium to further enhance vessel compliance. The safety and efficacy of OA has been shown in numerous clinical studies. This review will cover the MOA of OA, as well as the results of the associated clinical and economic studies.

Orbital atherectomy device description and mechanism of action. The Diamondback 360 (**Figure 2**) and Stealth 360 peripheral orbital atherectomy systems are designed to bi-directionally ablate/sand peripheral intimal plaque and impact deeper calcium in order to restore blood flow and improve vessel compliance in diseased peripheral arteries. The device is designed to track and spin over the ViperWire Advance and ViperWire Advance with Flex Tip guidewires (CSI). OA uses a single-use, low profile catheter attached to an electric handle, allowing for easy control of rotational and directional speed. The control knob mounted on the top of the handle allows the physician to track the catheter forward or backward in a controlled manner. Three speed selections can increase the rotational speed of the crown thereby increasing the orbital curve and ablation efficiency. The crown is available in three styles (classic, solid, and micro) and sizes ranging from 1.25 mm to 2.00 mm; the crown size is selected based on its ability to cross the lesion within the minimum proximal reference vessel diameter at the treatment site. The Diamondback 360 Exchangeable Series allows physicians to use multiple crowns with one handle to treat multilevel disease cases; cartridges are available with various crown size and shaft length configurations. Recently, Mustapha and colleagues published a systematic review with an emphasis on combined inflow and outflow revascularization.[17]

The eccentrically mounted crown is attached to the distal end of the catheter; when the catheter rotates at high speeds, centrifugal force pulls the mass of the crown toward the vessel wall in a circular orbit **(Figure 3)**. The centrifugal force equals the mass of the crown times the square of rotational velocity divided by the radius of the orbit. Since the radius of the orbit is fixed within the confines of an arterial wall, force increases to the second power as velocity increases. Thus, allowing the operator to control the degree of lesion modification, a mode of control not offered by any other form of atherectomy. By changing rotational speed, the operator can change the amount of force exerted on the vessel wall or the effective radius of orbit. Despite the abrasiveness of the crown, intimal damage to the vessel is minimized during the procedure because of a phenomenon called differential sanding. During the operation, the healthy elastic tissue flexes away from the crown, while calcified or fibrous material is engaged by the crown and sanded down. The orbital mechanism allows for continuous flow of blood and saline during treatment, minimizing the risk of thermal damage to the vessel wall which can be a cause of restenosis. The size of particulate generated is generally smaller than a red blood cell and is small enough to be absorbed by the reticuloendothelial system.

The orbital atherectomy MOA also exerts pulsatile forces via the repeated striking of the crown on the vessel wall (**Figure 3**; white arrow) as it orbits around the internal surface of the vessel.[18] Specifically, as the crown rotates 60,000-140,000 rpm, the offset portion of the crown rhythmically strikes the vessel wall, creating pulsatile energy[18] (aka, shockwaves) that may penetrate and impact deeper calcification. These micro-fractures/cracks may further improve the compliance of the vessel, allowing for low-pressure angioplasty while minimizing tissue damage and bailout stenting.

Also, the lesion modification described above may help to improve drug uptake into the vessel wall when drug-coated/eluting technologies are utilized post orbital atherectomy. Briefly, a cadaver study published by Tzafriri et al showed that calcified plaque limited intravascular drug delivery.[19] The authors showed that absorption rate varied inversely with pre-treatment calcium scores, and that OA treatment improved diffusivity in the lesion by an average of 70%.

Orbital atherectomy clinical trials and economic analyses. Orbital atherectomy clinical trials have shown that OA minimizes angiographic complications (**Figure 4**) and vessel damage, reducing the need for bailout stenting (**Figure 5**), a potential cause of restenosis. Below is a review of the supporting clinical trial data.

OASIS Trial. OASIS (Orbital Atherectomy System for the Treatment of Peripheral Vascular StenosIS) was a multicenter, single arm, investigational device exemption trial designed to assess the safety and efficacy of OA for treating chronic infra-popliteal arterial occlusive disease in PAD and CLI patients and enrolled 124 patients.[20] The primary safety endpoint was major adverse events (MAE), defined as death, myocardial infarction, amputation, or

FIGURE 2. Crowns shown are the 1.25 mm Micro Crown, 1.50 mm Classic Crown, and 2.00 mm Solid Crown. Photographs are not to scale and for illustrative purposes only. ©2020 Cardiovascular Systems, Inc. Images are used with permission from Cardiovascular Systems, Inc. CSI and Diamondback 360 are registered trademarks of Cardiovascular Systems, Inc.

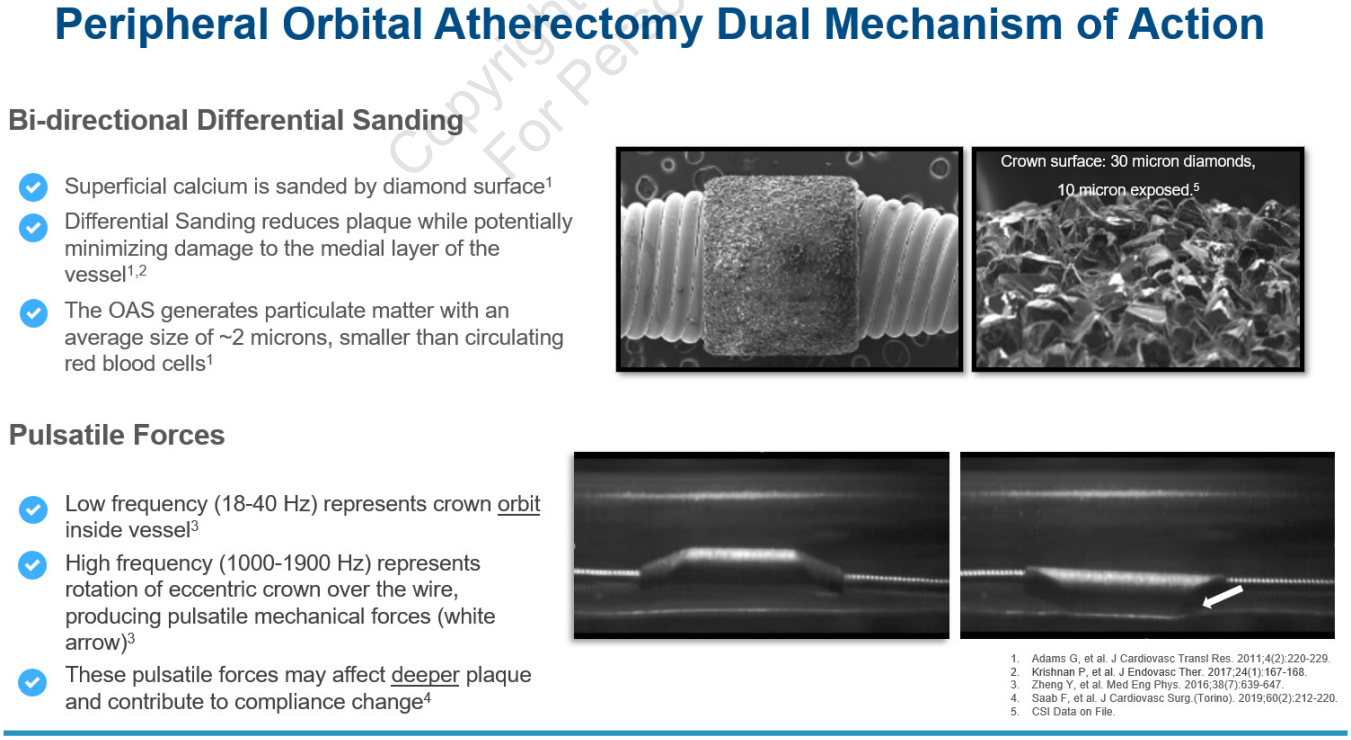

FIGURE 3. ©2020 Cardiovascular Systems, Inc. Images are used with permission from Cardiovascular Systems, Inc. CSI and Diamondback 360 are registered trademarks of Cardiovascular Systems, Inc.

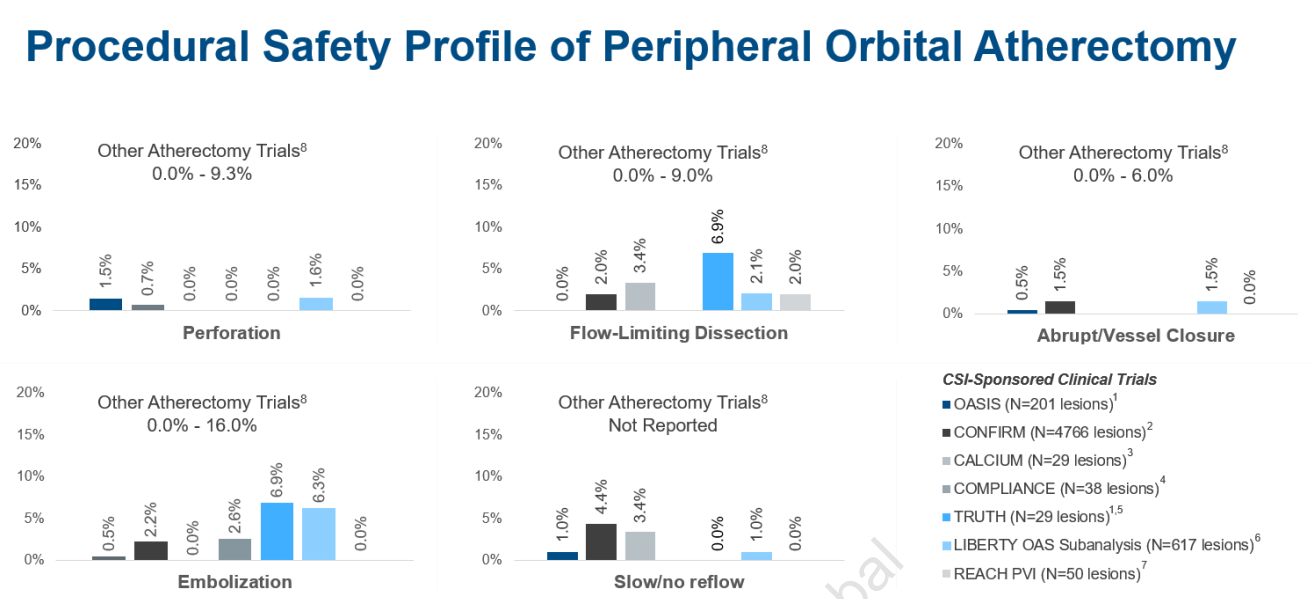

FIGURE 4. [1]CSI data on file. [2]Das T, et al. *Catheter Cardiovasc Interv.* 2014;83:115-22 and CSI Data on file. (Flow-limiting dissections and embolization were not tracked in 1146 lesions). [3]Shammas NW, et al. *J Endovasc Ther.* 2012;19:480-488. [4]Dattilo R, et al. *J Invasive Cardiol.* 2014;26:355-60. [5]Babaev A, et al. *Vasc Endovascular Surg.* 2015;49:188-94 and CSI data on file. [6]Giannopoulos S, et al. *J Endovasc Ther.* 2020;1526602820935611 and CSI data on file (21-May-2018 data). [7]Lodha A. REACH PVI Clinical Study Results. Presented at NCVH 2020. [8]Martinsen B, Evaluation and Use of Atherectomy Devices for CLI in US, Japan, and EU: Industry View VIVA 2017. (Includes directional, rotational, laser).

repeat revascularization, at 30 days and occurred in 3.2%. Procedural success (final diameter stenosis ≤30%) was achieved in 90.1% of cases. At 6 months the MAE rate was 10.4%. The authors of the OASIS study concluded that OA is a safe and unique approach to revascularization of the infrapopliteal arterial circulation in patients with chronic limb ischemia. Short-term data demonstrated substantial symptomatic improvement and infrequent need for further revascularization or amputation.

CONFIRM Registry Series. The purpose of the CONFIRM registry series was to evaluate the use of OA in lower extremity peripheral arteries and to optimize the treatment technique using the device.[21] Three peripheral OA device iterations were assessed: CONFIRM I evaluated the use of the Diamondback 360 exclusively (N=733 subjects), CONFIRM II evaluated Predator 360 (N=1127 subjects), and CONFIRM III evaluated Diamondback 360, Predator 360 and Stealth 360 (N=1275 subjects). The only requirement for enrollment was medically necessary treatment in accordance with the OA Instructions for Use. In the study, 35.4% of patients were claudicant Rutherford class three, and 42.7% had critical limb ischemia, Rutherford classes 4-6.[21] Overall complication rates were low, the most common was dissection (11.3%). Balloon angioplasty and stenting were used in 73.3% and 5.7% of lesions treated, respectively. Plaque removal was lowest in soft plaques (41%) and highest in severely calcified lesions (54%).[21] Interestingly a change in OA treatment strategy was noted over time, including changes in OA run time and crown sizes used. CONFIRM I had a significantly longer OA run time compared to CONFIRM II and III, and the crown sizes used in CONFIRM II and III were smaller than the crowns used in CONFIRM I. Both of these trends corresponded with a downward trend in procedural complications throughout the registry series, including lower rates of slow flow, vessel occlusion and spasm. The authors of the CONFIRM registry series concluded that a change in device usage to shorter spin times and smaller crowns across the study series corresponded to a lower incidence of adverse events (slow flow, vessel closure, and spasm) regardless of calcium burden or co-morbidities. These results suggest that vessel compliance change rather than luminal gain should be the goal of atherectomy.[21]

CALCIUM 360 Trial. CALCIUM 360 was a prospective, multicenter, randomized controlled trial to evaluate OA with adjunctive balloon angioplasty (BA) vs BA-only for treatment of calcified infrapopliteal lesions in 50 patients with CLI.[22] The adjunctive balloon inflation pressure was significantly lower in the OA+BA group (5.9 vs 9.4 atm; $P<.001$) and use of orbital atherectomy was associated with numerically fewer dissections and lower bail-out stenting.[22] Procedural success was numerically higher in the OA+BA group compared to BA-only (93.1% vs 82.4%; $P=.27$). At 12 months, the OA+BA group had significantly higher freedom from MAE (93.3% vs 57.9%; $P=.006$) and higher freedom from all-cause mortality (100% vs 68.4%; $P=.01$); however, freedom from target-vessel revascularization rates were similar (93.3% vs 80.0%; $P=.14$).[22] The authors of the CALCIUM 360 trial concluded

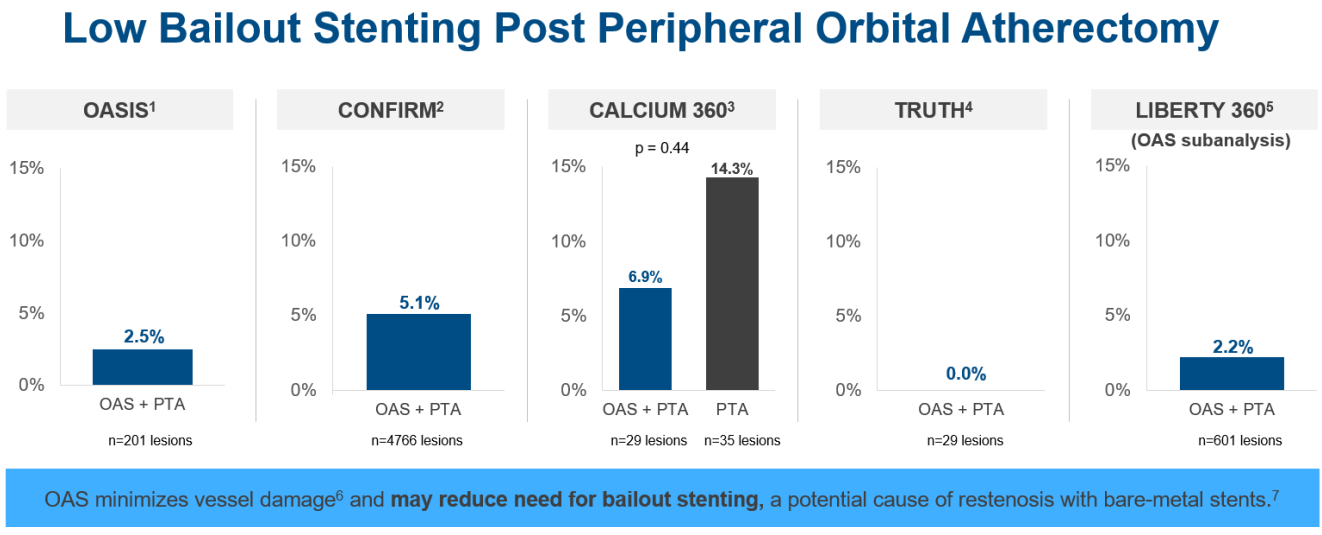

FIGURE 5. [1]CSI Data on file (Any adjunctive stenting). [2]CSI Data on file (Stenting due to dissection). [3]Shammas NW, et al. *J Endovasc Ther.* 2012;19:480-488. (Stenting for >30% residual stenosis, type C-F dissection, or significant recoil). [4]Babaev A, et al. *Vasc Endovascular Surg.* 2015;49:188-94. (Stenting due to dissection). [5]Giannopoulos S, et al. *J Endovasc Ther.* 2020;1526602820935611. [6]Krishnan P, et al. *J Endovasc Ther.* 2017;24(1):167-168. [7]Spreen M, et al. *Circ Cardiovasc Interv.* 2016; 9:e002376.

that vessel preparation with OA appears to increase the chance of reaching a desirable angioplasty result, with less acute need for bailout stenting with higher procedure success.

CALCIUM 360 Trial economic analysis. The incremental cost of peripheral OA plus BA vs BA-only for critical limb ischemia was estimated using CALCIUM 360 trial data.[23] Briefly, a deterministic simulation model used clinical and healthcare utilization data from the CALCIUM 360 trial and current cost data. Incremental cost of OA+BA vs BA-only included differential utilization during the procedure and adverse-event costs at 3, 6, and 12 months. For every 100 procedures, incremental annual costs to the hospital were US$350,930 lower with OA+BA compared with BA-only.[23] In addition, in a probabilistic sensitivity analysis, cost savings were observed in 81.6% of the Monte Carlo simulations, indicating that OA+BA was a dominant treatment strategy.[23] Despite higher upfront costs of OA, savings were realized due to reduced need for revascularization, amputation and end-of-life care over 6–12-month postoperative period. Thus, atherectomy with OA prior to BA was associated with cost savings to the hospital.[23]

COMPLIANCE 360 Trial. COMPLIANCE 360 was a prospective, multicenter, randomized controlled trial comparing acute and long-term outcomes of using OA and BA vs BA-only.[24] Fifty patients presenting with Rutherford class 2-4 and femoropopliteal calcified lesions were randomized 1:1 into the two study arms: OA+BA vs BA-only. Balloon inflation pressure was significantly lower in the OA+BA group vs BA-only (4 vs 9.1 atm; *P*<.001), consistent with the findings in the CALCIUM 360 trial. All lesions in both cohorts were treated without adjunctive stenting as a standard unless to address a suboptimal result. Procedural success (residual stenosis < 30% without adjunctive stenting) occurred in 86.8% of lesions in the OA treatment group vs 18.5% in the BA-only group (*P*<.001). At 6 months freedom from TLR (including adjunctive stenting) or restenosis was significantly higher in the OA+BA group (77.1% vs 11.5%; *P*<.001).[24] The authors of the CALCIUM 360 study concluded that compared to BA alone for the treatment of calcium-containing femoropopliteal lesions, OA pretreatment likely improves lesion compliance and leads to better luminal gain with lower balloon pressures, resulting in a marked reduction of adjunctive stenting.[24] Patency at 12 months with OA therapy is similar to a provisional stent strategy despite minimal stent usage. Avoidance of in-stent restenosis and preserving future treatment options, by not placing a stent, are key advantages of the OA therapeutic approach.[24]

COMPLIANCE 360 Trial Economic Analysis. The clinical outcomes from the COMPLIANCE 360 trial (OA+BA vs BA-only for treatment of calcified femoropopliteal lesions) were correlated with cost data and previously published quality of life data.[25] Site of service, hospital charges, and associated medical resource utilization were obtained from Uniform Billing statements for index treatments and associated revascularizations out to 1 year. Hospital costs were estimated using hospital-specific, procedure-specific cost-to-charge ratios. Length of stay and procedural data were collected from participating study sites. Twenty-five subjects with 38 lesions and 25 subjects with 27 lesions were randomized to the OA+BA and BA-only groups,

respectively. Mean hospital charges (US$51,755 vs US$39,922) and estimated hospital costs (US$15,100 vs US$11,016) were numerically higher for OA+BA compared with BA-only. Stent utilization was significantly higher with BA-only treatment for all subjects (1.1 vs 0.1; *P*=.001) and in the subset of subjects with one lesion (1.0 vs 0.1; *P*<.001).[25] There was a significant difference in cost for single-lesion vs multiple-lesion treatment. Using costs and quality-adjusted life years (QALYs) for the single-lesion cohort, the 1-year incremental cost of OA+BA vs BA-only was US$549, and incremental QALY was 0.16.[25] This resulted in an incremental cost-effectiveness ratio of US$3,441, well below the US$50,000 threshold. One-year index procedure cost and cost-effectiveness were comparable for OA+BA vs BA only.[25] This study provides compelling cost-effectiveness data for using atherectomy for treatment of calcified femoropopliteal lesions, a longstanding challenge for peripheral artery disease interventionalists.[25]

TRUTH study. The Tissue Removal Assessment with Ultrasound of the SFA and Popliteal (TRUTH) study assessed the performance of orbital atherectomy to treat femoropopliteal arteries, including determining its effect on plaque removal.[26] Twenty-five patients with >70% stenosis in SFA, POP, or TPT arteries were enrolled at single center. Intravascular ultrasound (IVUS) images were collected pre- and post-OA and post-OA and BA. The mean maximum balloon inflation pressure was 5.2 ± 1.2 atm.[26] Virtual histology IVUS (VH-IVUS) analysis revealed that at the maximum calcium ablation site calcium reduction was responsible for 86% of the lumen area increase.[26] The minimum lumen area increased from 4.0 mm^2 to 9.1 mm^2 (*P*<.001), and the percentage of area stenosis decreased from 76.9% to 43.0% (*P*<.001) after OA+BA.[26] At 12 months, the target-lesion revascularization rate was 8.2%, and ankle–brachial index and Rutherford classification improved significantly from baseline through follow-up. The authors concluded that the VH-IVUS analysis revealed that OA modifies the calcified component of the plaque burden. They further hypothesized that calcium modification by OA changes the lesion compliance, allowing for low pressure adjunctive BA.[26]

Lastly, a *post hoc* assessment of the TRUTH IVUS data was also completed to examine OA-mediated vessel wall injury. Briefly, the IVUS images were analyzed before and after OA for signs of a monolayer appearance of the arterial wall, which indicates disappearing medial and intimal layers and external elastic lamina.[27] The analysis revealed that only 2 cases in the post-OA images indicated medial injury, suggesting that OA can treat calcific plaque while minimizing medial injury. The authors indicated that these promising results warrant additional studies to further understand the mechanism of action of OA and its impact on the medial layer of the vessel being treated. It was also concluded that the IVUS assessment methods described in the *post hoc* analysis may also be used by operating physicians to detect medial injury intraprocedurally and alter treatment strategy for possible adjunctive antirestenosis therapy with drug-eluting technologies.[27]

LIBERTY Trial. LIBERTY was a prospective, observational, core laboratory–assessed, multicenter trial of endovascular device intervention in 1204 subjects (mean age 69.8±10.7 years; 770 men) stratified by Rutherford category (RC): claudicants (RC2-3; n=501) and CLI with no/minimal tissue loss (RC4-5; n=603) or significant tissue loss (RC6; n=100).[28,29] Key outcomes included quality of life (QoL) measures (VascuQol and EuroQol EQ-5D) and freedom from MAE, defined as death (within 30 days), major amputation, and target vessel revascularization (TVR) based on Kaplan-Meier (KM) analysis. The LIBERTY study design, endpoints, and data analysis plan were previously described in detail.[29] Below we review some of the recently published LIBERTY results.

LIBERTY Trial 1-year results. Successful revascularization was beneficial, with RC improvement noted across all groups.[28] Thirty-day freedom from MAE estimates were high across all groups: 99.2% in RC2-3, 96.1% in RC4-5, and 90.8% in RC6. At 12 months, freedom from MAE was 82.6% in RC2-3, 73.2% in RC4-5, and 59.3% in RC6 patients.[28] Estimates for freedom from major amputation at 12 months were 99.3%, 96.0%, and 81.7%, respectively.[28] QoL scores improved significantly across all domains in all groups with 12-month VascuQol total scores of 5.3, 5.0, and 4.8 for RC2-3, RC4-5, and RC6, respectively.[28] The results indicate that peripheral endovascular intervention is a viable treatment option for RC2-3, RC4-5, and RC6 patients as evidenced by the high freedom from major amputation, as well as the improvement in QoL and the RC at 12 months. Furthermore, primary unplanned amputation is often not necessary in RC6.[28]

LIBERTY Trial 1-year CLI subanalysis. For this LIBERTY CLI subanalysis, RC5 and RC6 patients (RC5-6; N=404) were pooled and 1-year outcomes were assessed.[30] Procedural complications rarely (1.7%) resulted in postprocedural hospitalization and 89.1% of RC5-6 patients were discharged to home. Considering the advanced disease state in RC5-6 patients, there was a high freedom from 1-year MAE rate of 65.5%.[30] At 1 year, freedom from major amputation was 89.6%. Wounds identified at baseline on the target limb had completely healed in 172/243 (70.8%) of the RC5-6 subjects by 1 year. Additionally, the overall quality of life, as measured by VascuQoL, improved from baseline to 1 year.[30] This analysis of LIBERTY RC5-6 patients demonstrates that peripheral endovascular device intervention can be successful in CLI patients, with low rates of major amputation and improvement in wound healing and QoL through 1-year follow-up.

LIBERTY Trial 3-year results. The 36-month KM survival rates were 86.0% in RC2-3, 79.8% in RC4-5, and 62.0% in RC6 groups.[31] The KM estimates of freedom from major amputation at 36 months were 98.5% in RC2-3, 94.0% in RC4-5, and 79.9% in RC6. The 36-month KM estimates for freedom from TVR were 71.1% in RC2-3, 64.2% in RC4-5 and 61.9% in RC6 groups.[31] Patients with claudication at baseline were at lower risk for MAEs compared with RC4-5 and RC6

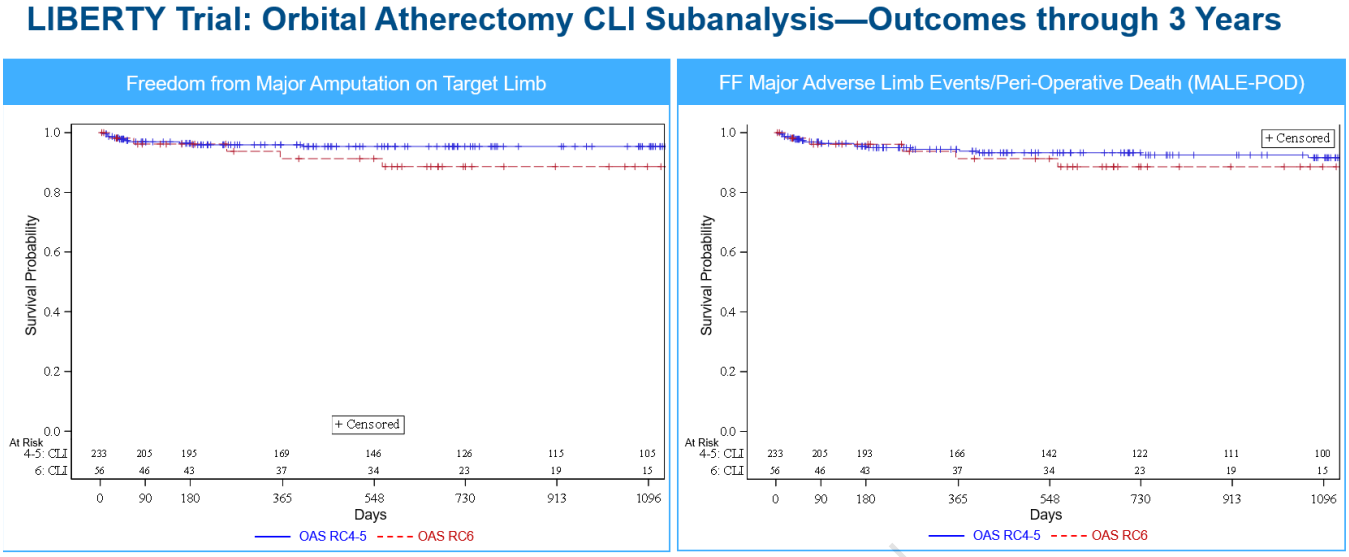

FIGURE 6. Mustapha J. LIBERTY 360 3-Year Data. Presented at AMP 2019. Amputation Free Survival: Freedom from major amputation on target limb or death. MALE-POD: Major Adverse Limb Events include major reintervention of the target vessel (surgical bypass), major amputation of the target limb, or perioperative death. Kaplan-Meier method used to obtain estimate rates. 28-May-2019 Data.

patients during the 36-month follow-up. Vascular QoL improved from baseline and persisted up to 36 months in all patients.[31] The results indicate that endovascular therapy is a viable treatment option for patients with symptomatic PAD, with sustained improved quality of life in both claudicants and patients with chronic limb-threatening ischemia through 3-years.[31]

LIBERTY Trial 3-year orbital atherectomy subanalysis. Analysis of the LIBERTY trial identified 503 PAD patients with a total of 617 femoropopliteal and/or infrapopliteal lesions treated with any commercially available endovascular devices and adjunctive OA: RC2-3 (n=214), RC4-5 (n=233), or RC6 (n=56). The mean lesion lengths were 78.7 ± 73.7, 131.4 ± 119.0, and 95.2 ± 83.9 mm, respectively, for the 3 groups.[32] After OA, balloon angioplasty was used in >98% of cases, with bailout stenting necessary in 2.0%, 2.8%, and 0% of the RC groups, respectively. A small proportion (10.8%) of patients developed angiographic complications, without differences based on presentation. During the 3-year follow-up, claudicants were at lower risk for MAE, death, and major amputation/death than patients with CLI. The 3-year KM survival estimates were 84.6% for the RC2-3 group, 76.2% for the RC4-5 group, and 63.7% for the RC6 group.[32] The 3-year freedom from (FF) major amputation was estimated as 100%, 95.3%, and 88.6%, respectively.[32] **Figure 6** shows the FF major amputation KM curve for the CLI subset. In addition, a contemporary endpoint of FF major adverse limb events-perioperative death (MALE-POD) is shown in **Figure 6**, indicating durable OA results from 1-year through 3-years in the CLI patient population (RC4-5: 94.4% to 91.6%, RC6: 91.3% to 88.6%).

Lastly, among CLI patients only, the RC at baseline was correlated with the combined outcome of major amputation/death, whereas RC classification did not affect TVR, MAE, major amputation, or death rates. The overall results indicate that peripheral artery angioplasty with adjunctive OA in patients with CLI or claudication is safe and associated with low major amputation rates after 3 years of follow-up.[32] These results compare favorably with a Medicare claims data analysis of atherectomy which showed a 3-year mortality rate of 40.1% and amputation rate of 6.4% in the CLI patient population.[33]

Conclusions

The dual mechanism of peripheral orbital atherectomy (bi-directional differential orbital sanding and pulsatile forces) provides an effective and safe treatment of peripheral atherosclerotic lesions with varying levels of occlusion and calcification. The combination of plaque modification, improved vessel compliance, and lumen enlargement via OA can effectively restore blood flow in vessels above- and below-the-knee, relieving symptoms and improving limb salvage rates in patients with PAD and CLI. Numerous peripheral OA clinical trials have confirmed the high rates of procedural success, freedom from major adverse events, and freedom from amputation, as well as the economic value of orbital atherectomy.

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