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January 2022

The Impact Of Clinical Follow-Up After Revascularization On The Outcomes Of Patients With Chronic Limb Threatening Ischemia

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The Impact of Clinical Follow-up after Revascularization on the Outcomes of Patients with

Chronic Limb Threatening Ischemia

A Thesis Submitted to the Yale University School of Medicine in Partial Fulfillment of the

Requirements for the Degree of Doctor of Medicine

by

Gathe Kiwan Class of 2022

Acknowledgements:

A special thanks is due to my thesis advisor Dr. Cassius Iyad Ochoa Chaar for agreeing to work with me and to advise me throughout medical school. His unwavering support of my education and career advancement has meant the world to me.

I would also like to thank Alaa Mohamedali for her help with achieving this project as well as Dr. Tanner Kim who was always available to help when needed. I also appreciate Haoran Zhuo whose help with statistical analyses was crucial to the completion of this study.

Finally, a thanks to my mother, father, and life-partner Luna for their endless support of me in everything I do.

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ABSTRACT

Objective: Guidelines for optimal follow-up for patients undergoing lower extremity

revascularization (LER) for peripheral arterial disease (PAD) recommend multiple visits with

imaging during the first year followed by yearly monitoring thereafter. Patients with chronic

limb-threatening ischemia (CLTI) are at greater risk for mortality and major amputation than

patients treated for claudication and thus necessitate closer monitoring. The goal of this paper is

to study the effects of compliance with follow-up after revascularization for patients with CLTI

on major amputation rates and mortality.

Methods: A single-center retrospective chart review of consecutive patients undergoing LER for

CLTI was performed. Patients were stratified based on compliance with follow-up to compliant

or non-compliant cohorts. Patient characteristics, reinterventions, and perioperative and long-

term outcomes were compared between the two groups.

Results: There were 356 patients undergoing LER for CLTI and 61% (N=218) were compliant.

There was no significant difference in baseline characteristics between the two groups. Non-

compliant patients were more likely to undergo endovascular interventions compared to

compliant patients (92.8% vs 79.4%, P=.03). There was no difference in perioperative outcomes

between the 2 groups with overall 30-day mortality of 0.6%. After mean follow up of 2.7 years,

compliant patients had greater ipsilateral reintervention rates (49.1% vs 34.1%, P=.005) as well

as overall reintervention rates (61% vs 44.2%, P= 0.002) compared to non-compliant patients.

There was no significant difference in mortality or ipsilateral major amputations between the 2

groups.

Conclusions: Patients who were compliant with follow-up after LER for CLTI underwent more

reinterventions with no difference in mortality or major amputation. Further research regarding

the threshold for reintervention as well as the optimal schedule for follow up in patients with CLTI is needed.

1. Introduction:

Peripheral artery disease (PAD) is a progressive disease that affects 8-10 million Americans over 40 years of age, and 12-20% of Americans above the age of 65. Additionally, there are 500-1,000 per million new cases of critical limb-threatening ischemia (CLTI) every year.[1-4] CLTI occurs when PAD progresses to an advanced stage resulting in more severe symptoms, often pain at rest or tissue loss, and is associated with worse outcomes. The presentation of CLTI varies widely and outcomes depend on the availability and quality of primary and secondary care. CLTI is associated with high morbidity and mortality with an estimated 12-month major amputation rate of 22% in untreated individuals.[5] Although CLTI represents the final stage of PAD progression, approximately half of patients presenting with CLTI have no known prior history of PAD.[6,7] Successful management of CLTI begins with timely diagnosis and medical management of relevant comorbidities. Growing evidence shows that optimizing medical management of patients with PAD improves vessel patency and mortality.[8-10] Next, lower extremity revascularization (LER) is performed according to the anatomy and severity of disease. Options for interventions are broadly categorized to either open surgery or endovascular treatment (EVT). The number of techniques for treatment of CLTI with minimally invasive EVT has increased in recent years and has led some to advocate an "endovascular-first" approach for most patients with CLTI. However, evidence from ongoing trials argues for the use of selective revascularization algorithms based on specific criteria.[11-13] In practice, the frequency of EVT use for treatment of PAD has increased dramatically and has surpassed that of open surgical approaches.[14-18]

It is generally accepted that achieving optimal outcomes after open surgical and endovascular procedures requires clinical follow-up. All vascular procedures have modes of failure that must be identified and managed in a timely manner. Optimal follow-up after LER allows for the detection of recurrent disease and other complications at an early stage when they can be managed safely and effectively even before clinical signs occur. Follow-up also offers the opportunity to optimize pharmaceutical therapy, smoking cessation, pain management, and diet and exercise. The Global Vascular Guidelines for management of CLTI recommend performing a thorough interval history and a physical exam with complete examination of the foot including assessment of neuropathy and a probe-to-bone test of any open ulcer in patients with tissue loss. Furthermore, measurement of the ankle-brachial index (ABI) is recommended as the first-line noninvasive test for diagnosis and surveillance of CLTI. Non-invasive arterial imaging is also recommended at follow-up visits using typical duplex ultrasound (DUS) with the use of computed tomography angiography (CTA), or magnetic resonance angiography (MRA) selectively.

While significant strides have been made to improve endovascular tools and techniques, data regarding post-operative management and follow-up protocol for patients with CLTI remains debatable. The Society for Vascular Surgery currently recommends DUS surveillance immediately after open lower extremity revascularization with continued follow-up at 3, 6, and 12 months and then every 6 to 12 months for life thereafter. As for endovascular therapies, the optimal time for follow-up has yet to be determined with recommendations of follow-up varying based on the clinical picture and severity of disease.[19] The American College of Cardiology and American Heart Association task force recommends periodic follow up for patients with CLTI to monitor treatment response, symptom progression, and cardiovascular risk . However, the

current guidelines for interventional cardiologists and interventional radiologists do not provide an ideal follow-up timeline or protocol leaving the choice of timing and surveillance imaging largely to the individual provider.[20] Moreover, studies aiming to optimize follow-up for endovascular treatments have yielded conflicting data putting in question the optimal method of surveillance after LER.[21-26] A recent study showed that patients who were lost to follow up at 1 year after undergoing endovascular intervention for PAD had worse long-term survival than those whose records indicated a follow-up visit was performed during the first post-operative year.[21]

Statement of Purpose:

This study focuses on the impact of compliance with a clinical follow up schedule for patients with CLTI undergoing LER on reintervention, major amputation, and mortality. Our hypothesis is that compliant patients have lower rates of major amputation and mortality compared to non-compliant patients.

2. **Materials and Methods:**

Student Contributions: the electronic medical records of a total of 356 patients who underwent LER for CLTI at Yale New Haven Hospital were reviewed by the writer and Alaa Mohamedali. The information gathered was recorded into a RedCap database, a HIPAA compliant server. After completion of data collection, the writer designed the study with the guidance of Dr. Cassius Iyad Ochoa Chaar. Dr. Tanner Kim was also involved in the design of the study and contributed as an advisor during the collection of data. Statistical analysis was performed by Haoran Zhuo with supervision and consultation of Dr. Yawei Zhang.

Ethics Statement: This thesis includes a retrospective cohort study that was done to better understand the impact of follow-up after LER for CLTI patients on the outcomes of revascularization. No live human subjects were harmed in the making of this thesis and private health information was carefully used according to the guidelines of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). The use of the word "compliance" in this study strictly refers to the adherence to a protocol of follow-up and is not meant to pass judgment or place blame on patients.

Human Subjects Research: This study was approved by the Yale University Institutional Review Board, and no patient consent was required.

2.1. Study Design

A retrospective review of the electronic medical records (EMR) of consecutive patients diagnosed with CLTI undergoing open or endovascular LER at Yale New Haven Hospitals by multiple providers from different specialties (vascular surgery, interventional cardiology, and interventional radiology) was performed. Patients with no records in the EMR after LER or who died within 3 months of the index procedure were excluded from this analysis. Patients were stratified according to their compliance with clinical follow-up into compliant and non-compliant groups: stratification was done at the time of data collection and entry into the database. Follow-up compliance after revascularization was defined as in-person follow-up visits with any vascular specialist addressing the perfusion status of the limb at least once during the first 3 months, and a second time in the following period of up to 15 months after the index procedure. Even though more frequent follow up, initially, and yearly lifetime visits have been advocated, these 2 visits were considered a minimal threshold for patients to qualify as "compliant". These 2 visits also corroborate with the vascular quality initiative (VQI) guide for minimal compliance

with long-term follow up that provides a window of 9 to 21 months to record follow up.[27] Any

patient who did not meet the criteria was considered non-compliant with follow-up. It is

important to note that compliance in this study strictly refers to adherence to the clinical visit

schedule. For example, patient that comes for their first follow-up visit more than 3 months after

the index procedure is considered non-compliant even if they continue to follow-up with a

clinician for years after the procedure. Furthermore, total follow-up time of an individual patient

was calculated as the time from the index procedure until the last recorded clinical visit in the

EMR. Post-operative adherence to best medical therapy, diet, exercise, smoking cessation, and

surveillance imaging were not recorded in this study. Follow up with primary care physicians or

other specialists that do not address the status of limb perfusion did not count towards

compliance but allowed the capture of information related to symptoms, major amputation, and

mortality. Patients that were admitted to the hospital and received follow up as inpatient only

without an outpatient visit with a vascular specialist after discharge were considered non-

compliant. Compliance with follow up was analyzed based on the first LER procedure in patients

who underwent additional reinterventions.

2.2. Patient characteristics:

Patient characteristics were individually reviewed, and data collected included patient

age, gender, race, comorbidities, and medications (aspirin, ADP/P2Y12 inhibitor,

anticoagulation medications, and statins). Patient's history of current or former smoking,

diabetes, chronic renal insufficiency (CRI) defined as baseline creatinine above 1.5 mg/dL or a

glomerular filtration rate of less than 60 mL/min, serum creatinine, end stage renal disease

(ESRD) requiring dialysis, hypertension, hyperlipidemia, coronary artery disease (CAD),

congestive heart failure (CHF), stroke, hypercoagulable disease, history of cancer, and history of

prior endovascular procedures or prior open procedures for LER were noted. All patient

characteristics were recorded as of the index procedure. Changes to patient characteristics after

the index procedure were not recorded.

2.3. Procedures

The first intervention in the EMR during the study period was captured and considered

the index procedure to assess compliance. Patients with records indicating interventions dating

prior to the establishment of EMR were carefully reviewed and any data available from pre-EMR

records pertaining to revascularization was recorded whether from manually inserted old records

or physician notes. Reinterventions were individually recorded in the database. The date of the

procedure, performing physician, indication (rest pain or tissue loss), and anatomical level was

captured. Procedure types were divided into either endovascular, open, or hybrid. Endovascular

therapies consisted of balloon angioplasty, stenting, and atherectomy. Open procedures were

divided into suprainguinal bypass, infrainguinal bypass or endarterectomy, typically of the

common femoral artery. Hybrid procedures included a combination of open and endovascular

LER.

2.4. Perioperative Outcomes

Complications within 30 days of the intervention were individually reviewed. The

following procedural complications were recorded: hematoma, pseudoaneurysm, bleeding,

wound infection, pneumonia, urinary tract infection, arterial thrombosis, deep vein thrombosis,

stroke, acute renal failure, acute need for hemodialysis, unplanned return to the operation room

within 30 days, major amputation, and death. Bleeding was defined as any transfusion

requirement or return to the operating room due to bleeding. Major amputation was defined as any amputation at or above the ankle.

2.5. Long-term Outcomes

Long-term follow-up outcomes were collected. Mean follow-up time in years for each study group was derived. The frequency of overall reinterventions as well as ipsilateral reinterventions were calculated. Reintervention rate was defined as the percentage of patients undergoing any other LER after the index procedure. The reintervention index was defined by the number of reinterventions recorded for patients divided by the years of follow up.[28] Long-term major amputation ipsilateral to the index limb treated and mortality were captured. Patients who had index procedures on bilateral limbs were considered to have an ipsilateral reintervention or major amputation if it occurred on either limb. Additionally, mortality was also recorded using the electronic medical record or social security death index.

2.6. Statistical Analysis

Continuous data was reported as mean ± standard deviation. Categorical data was reported as percentages. $P < 0.05$ was considered statistically significant. Differences between the two cohorts were compared using Chi-Square test for categorical variable and student t-test for continuous variables. Multivariable regression was performed to determine the factors associated with survival, ipsilateral reintervention, and major amputation. These factors included smoking, age, BMI, compliance with follow-up, diabetes, ESRD, CHF, and CAD.

3. Results

3.1. Patient Characteristics

There were 356 patients that underwent LER for CLTI. There were 218 (61.2%) patients who were compliant with follow-up. There were no significant differences in demographics, comorbidities, or medical management between patients who were compliant with follow-up and those who were not. (Table I)

3.2. Procedures

There were 61 index procedures for rest pain and 295 for tissue loss with no significant difference in indication between the 2 groups. Patients in the non-compliant group were more likely to have undergone an endovascular procedure compared to compliant patients (92.8% vs 79.4%, P=0.003). Also, patients in the compliant group were more likely to undergo infrainguinal bypass (13.3% vs 5.8%, P=.024) and common femoral endarterectomy (8.7% vs 2.2%, P=.013) compared to the patients in the non-compliant group. (Table II)

3.3. Perioperative Outcomes

There was no significant difference in the perioperative (30-day) outcomes observed between patients who were compliant with follow-up and those who were not. More specifically the overall rate of perioperative major amputation, any morbidity, and mortality were 3.6%, 25.3%, and 0.5% with no differences between the groups. (Table III)

3.4. Long-term Outcomes

The mean follow-up time was 2.7 ± 1.8 years with no significant difference between the 2 groups (P=0.202). Overall, 49.1% of compliant patients received an ipsilateral reintervention compared to only 34.1% of non-compliant patients (P=0.005). The average number of ipsilateral reinterventions in compliant patients was significantly higher at 2.2 ± 1.8 compared to 1.60 ± 1.1 in the non-compliant cohort (P=0.02). However, the reintervention index, after adjusting for time

of follow up, was not statistically significant (P= 0.419). Patients compliant with follow-up had a significantly higher overall reintervention rate compared to patients non-compliant with follow up (61% vs 44.2%, P=.002) and had more frequent overall mean number of reinterventions (2.7 ± 2.3 vs 2.1 ± 1.7, P=.036). There was a trend towards a higher reintervention index in non-compliant patients that did not reach statistical significance (1.8 ± 2.2 vs 1.2 ± 2.4, P=.094). There was no difference in mortality or major amputation between the 2 groups. (Table IV)

3.5. Risk Factors Associated with Ipsilateral Reintervention

Multivariable regression analysis was performed to examine the independent association of individual variables with ipsilateral reintervention during the study period. Increased age was associated with a decrease in the odds ratio of receiving ipsilateral reintervention (OR= 0.98 [0.96-1.00]). Compliance with follow-up was associated with significantly increased likelihood of receiving ipsilateral reintervention (OR= 1.82 [1.15-2.89]). Moreover, patients undergoing open, or hybrid procedures were found to have significantly decreased likelihood of receiving a reintervention (OR= 0.48 [0.27, 0.83]). (Table V)

3.6. Risk Factors Associated with Ipsilateral Major Amputation

Multivariable regression analysis was performed to examine the independent association of individual variables with major amputation of the ipsilateral index limb. Patients with ESRD had an increased odds ratio for ipsilateral amputation (OR= 4.16, CI [1.95-8.86]), while CHF was associated with decreased odds ratio for ipsilateral amputation (OR= 0.36 [0.14-0.95]). Furthermore, patients undergoing open, or hybrid procedures had a significantly increased likelihood of ipsilateral major amputation (OR= 2.59 [1.17, 5.77]). Notably, compliance with

follow-up showed no statistically significant association with receiving ipsilateral amputation in this analysis (P= 0.183). (Table V)

3.7. Risk Factors Associated with Mortality

Multivariable regression analysis was performed to examine the independent association of individual variables with mortality. Procedure modality did not show an association with mortality on regression analysis. Increasing age (OR= 1.05 [1.02-1.07]) and ESRD (OR=4.88 [2.38, 10.01]) were the only factors noted to be independently associated with increased mortality. Compliance with follow-up had no significant association with mortality (P= 0.179). (Table V)

4. Discussion

Clinical follow up is an essential element in the optimization of outcomes of patients after any vascular procedure. The role of follow-up is widely accepted in the medical community yet the data surrounding the effects of clinical follow-up on outcomes have not been consistently reported in the literature. In this study, patients who were compliant with the proposed follow-up schedule after LER for CLTI were found to have higher reintervention rates following the index procedure with no difference in mortality or major amputation rates. Compliant patients were more likely to have had open bypass procedures than patients who were non-compliant with follow-up. On regression analysis, open and hybrid procedures were associated with decreased reintervention. However, there was no association between compliance with follow up and the outcomes of major amputation and mortality. These findings raise the important question of whether compliance with follow-up yields better outcomes, and whether the current thresholds for reintervention and paradigms for follow up are optimal.

The current guidelines published by the Society for Vascular Surgery (SVS) confirm that there is still a pressing need for better clinical data on all aspects of follow-up after vascular surgery procedures.[19] Particularly, there is a need for data surrounding indications for reintervention, as well as duration, frequency, and modality of surveillance. Modalities for surveillance include clinical follow-up visits for symptom assessment by physical exam, ABI measurements, and DUS scan. Other imaging modalities such as digital subtraction angiography, CTA, and MRA are not recommended due to the higher cost, limited access, as well as the associated contrast dye and radiation exposure risks and should be used selectively.[29]

Currently, SVS guidelines strongly recommend clinical examination and ABI, with or without DUS in the early postoperative period after aortobifemoral, iliofemoral, femoral-femoral, and axillobifemoral bypass to provide a baseline for further follow-up. Afterwards, evaluation should be repeated at 6 and 12 months and then annually as long as patients are asymptomatic.[19] Patients with prosthetic infrainguinal bypass grafts should receive the same surveillance. DUS should be added to the surveillance regimen in patients who undergo infrainguinal vein graft bypass. Furthermore, an increased frequency of surveillance during the first postoperative year is recommended for these patients with evaluations in the perioperative period, and at 3, 6, and 12 months and at least annually thereafter. It is important to note that while these are strong recommendations, they are primarily based on low to moderate quality evidence.[19]

As for endovascular treatment (EVT), SVS guidelines also strongly recommend clinical examination, ABI, and DUS within the first month after aortoiliac segment EVT to provide a baseline and to evaluate for residual stenosis. Clinical examination and ABI with or without the addition of DUS should be performed at 6 and12 months and then annually as long as there are

no new signs or symptoms. A more frequent schedule is also suggested for EVT of the femoropopliteal and tibial segments with evaluations at 1, 3, and 6 months followed by evaluations every 6 months thereafter. To understand the rationale for these recommendations, it is appropriate to highlight some of the current literature on the outcomes of open and endovascular LER for CLTI, followed by available evidence for the frequency, duration, and modalities used for postoperative surveillance.

Outcomes of CLTI after Open Bypass:

The outcomes of CLTI after open bypass surgery has been extensively reported in the literature. However, quality studies reporting details regarding surveillance are scarce. Bypass surgery and endarterectomy have been performed for the treatment of CLTI and the outcomes of these procedures vary by anatomic location and bypass graft used. Aortobifemoral bypass patency rates are excellent and in the range of 88% to 93% at 3 to 5 years.[30,31] Iliofemoral bypass performed for unilateral iliac artery occlusive disease is performed as an alternative to femoral-femoral bypass to avoid bilateral groin incisions. Studies reporting long term follow-up outcomes list primary patency ranges of 61% to 66% at 5 to 8 years.[32,33] While secondary patency rates were as high as 80% to 93% at 5 years.[33,34] Femoral-femoral bypass can be performed for unilateral iliac artery disease and generally results in patency rates lower than those of aortobifemoral bypass. One prospective study reports a 5-year primary patency rate for this technique as 35% although details of surveillance methods were not clearly described.[35] Another study used DUS criteria to guide reinterventions in patients who had received femoral-femoral bypass saw an increase in 5-year primary patency and primary-assisted patency rate from 62% to 88%.[36] Axillobifemoral bypass is a technique performed in patients who cannot receive aortic reconstruction or those with a history of aortic graft infection. The SVS reports on

the paucity of literature addressing surveillance of this procedure. Cumulative patency rates of 85% to 87% at 3 to 4 years are reported with no details regarding surveillance modality or frequency.[37,38] Infrainguinal revascularization with vein graft is one of the most common procedures for CLTI LER.[19] There are multiple modes of failure and complications as well as timelines for these failures. The bypass is at risk of early, midterm, or late failure. Early failure (within 30 days is generally due to technical issues during surgery. Midterm failure (30 days to 2 years) may be due to intimal hyperplasia affecting the conduit or anastomosis. Late failures (after 2 years) often occur as a result of atherosclerosis progression affecting the inflow and/or outflow vessels.[39]

Outcomes after EVT:

With the constant development of endovascular and minimally invasive devices, EVT has been an attractive option for treatment of CLTI. Options for EVT treatment include plain balloon angioplasty, stenting (bare metal, covered, and drug-eluting), and atherectomy. Several studies have reported on the long-term outcomes and natural history of CLTI after EVT. The most important complication for EVT of CLTI is restenosis. The specific pathophysiology involved in restenosis is not yet fully understood. However, it is largely believed that inflammation due to injury to arterial smooth muscle cells, endothelium, and thrombus deposition plays a key role in restenosis after EVT.[40] Moreover, one study examining this phenomenon explains that restenosis may occur as arterial remodeling and/or neointimal hyperplasia.[41] These authors observed that restenosis after balloon injury was due to a combination of arterial remodeling and neointimal hyperplasia, while restenosis after stenting consisted mostly of neointimal hyperplasia. Furthermore, the neointimal hyperplasia was observed to be more significant in the stent group when compared with the balloon group.

Midterm and long-term outcomes for EVT of aortoiliac disease have been excellent. 5-year primary patency rates were reported to be 64% to 82%.[42-44] A large retrospective study reported primary patency of aortoiliac stenting in 2096 patients to be 93%, 83%, and 78% at 1 year, 3 years, and 5 years, respectively. [45] As in the case of open procedures, reports of DUS surveillance after aortoiliac EVT are rare in the literature. One such study reported 72 cases of iliac artery balloon angioplasty which were surveyed by DUS at 1 month, 3, months, and 1 year.[46] Results of the study showed that patients with DUS determined residual stenosis or restenosis were not significantly different from those with normal findings on DUS.

Femoropopliteal segments are commonly treated by EVT. One study examining outcomes of patients receiving femoropopliteal EVT for CLTI reported primary and secondary patency rates of 41% and 79%, respectively.[47] A retrospective study reviewing 330 cases of superficial femoral artery stenting monitored by DUS derived criteria to help determine which patients have significant restenosis.[48] The authors concluded that the peak systolic velocity (PSV) and velocity ratio (Vr) measured by DUS correlate with in-stent restenosis and may predict it with high specificity. The VIBRANT trial compared the long-term outcomes of complex superficial femoral artery disease treated with covered Viabahn stents and those of bare-metal nitinol stents.[49] More than 30% of patients in both groups received at least on reintervention. Primary patency rates at 3 years were similar and low for both at 24% and 26%, respectively. However, bare metal stents had better primary-assisted patency than Viabahn stents at 89% vs 70%, P= 0.04, and similar secondary patency 89% vs 80%, P=0.304. The authors concluded that patients who have received complex femoropopliteal stenting would benefit from a rigorous surveillance program, particularly during the first postoperative year. This is due to the rapid decline of patency rates observed during the first year of device implantation. In-stent

restenosis poses a significant challenge in the management of CLTI in femoropopliteal segments. A study by Armstrong et al observing patients receiving EVT for femoropopliteal in-stent restenosis (ISR) reported that the angiographic characteristics of femoropopliteal ISR were significantly associated with long-term outcomes. Moreover, patients with CLTI had significantly worse outcomes than patients with claudication. After 2 years of follow-up, patients treated with EVT for total occlusion of stents (Class III ISR) had the highest risk of recurrent ISR (HR 2.4, 95% CI 1.1–5.6) and recurrent occlusion (HR 5.8, 95% CI 1.8–19.0) compared to other types of ISR.

EVT for tibial revascularization is almost exclusively used in cases of CLTI.[19] It has been proven that tibial segment EVT is effective in significantly reducing major amputation rates in CLTI. In study describing 417 diabetic CLTI patients with ischemic foot ulcers undergoing lower-limb subtraction angiography, 63% of cases had diffuse lesions with occlusion of 3 arteries and multiple stenoses of the tibioperoneal and/or femoropopliteal segment.[50] Because most cases of tibial revascularization reported in the literature included treatment of lesions extending towards the proximal femoral and popliteal segments, an accurate evaluation of tibial revascularization outcomes is challenging. In a report focusing purely on tibial segments, limb salvage at 3-5 year follow-up was 72-98% and average primary patency was reported at 55% at 6-24 months.[51] Saqib et al examined the outcomes and predictors of restenosis for EVT of the tibial arteries.[52] DUS surveillance was used to determine restenosis. In patients with worsening wounds, angiography was used regardless of DUS findings. Tibial artery restenosis or occlusion was observed in 41% of limbs. Restenosis or occlusion significantly increased the risk of major amputation (27% vs 4%). Furthermore, the need for further reintervention for patients receiving repeated EVT was observed to be higher than those who received open bypass reintervention.

Additionally, studies have compared the outcomes of different EVT and open bypass techniques on the treatment of PAD. One such was a meta-analysis conducted by Almasri et al in 2018 evaluating relevant outcomes of infrainguinal revascularization procedures in patients with CLTI. They found that patency rates are highest for saphenous vein bypass, whereas both patency and limb salvage are markedly inferior for prosthetic grafting of below the knee segments. Among endovascular interventions, percutaneous transluminal angioplasty and drug-eluting stents appear comparable for focal infrapopliteal disease. The authors state, however, that heterogeneity in patient risk, severity of limb disease, and anatomy renders any comparison difficult to make from a retrospective study. The BASIL trial was a multi-center randomized controlled trial wherein 452 patients with CLTI were randomized to either balloon angioplasty (n= 228) treatment or bypass surgery (n= 224) for treatment of infrainguinal disease.[53] All patients were followed for at least 3 years. Results showed that patients randomized to balloon angioplasty had higher immediate technical failure than those receiving bypass surgery (20% vs 2.6%; P= 0.01). Outcomes of vein bypass grafts were better than prosthetic grafts for amputation-free survival (P= 0.003) but not for overall survival (P= 0.38). The authors also found that patients who received bypass surgery after failed balloon angioplasty had significantly worse survival than those who received bypass surgery as a first revascularization. However, the trial also noted that balloon angioplasty appeared overall superior to prosthetic graft bypass surgery. The authors of the BASIL trial published a clinical tool to predict the survival of patients with CLTI based on patient characteristics which may be used when deciding on a treatment and surveillance modality.[54]

ABI utility in CLTI:

The ABI is a measurement that provides objective data that serves as the first-line modality for the diagnosis of lower extremity PAD. It is a relatively simple and cost-effective tool that offers prognostic data that are useful to predict limb survival, wound healing, and patient survival. The ABI can be used in initial diagnostics of disease but also as a surveillance tool to monitor the efficacy of therapeutic interventions.[55] An abnormal ABI value may offer the physician useful information when assessing the risk of a patient for disease progression. For example, one study reports that patients with an ABI value less than 0.40 are more likely to experience rest pain, and hence, progression to CLTI.[56] Conversely, an ABI value greater than 0.50 suggests that progression to CLTI is unlikely during the subsequent 6.5 years.[57] However, ABI values exceeding 1.40 were reported to carry a higher hazard of cardiovascular related mortality.[58] Indeed, the relationship between the ABI and atherosclerosis risk factors has been confirmed, as well as the link between abnormal ABI and cardiovascular and cerebrovascular disease.[59] In a study which included 1537 elderly men and women, low ABI was predictive of total and cardiovascular mortality with an increased relative risk of up to 4-fold.[60]

Lijmer et al used a receiver operating characteristic (ROC) analysis to determine the diagnostic accuracy of ABI in patients with femoropopliteal and infrapopliteal disease. The authors concluded that ABI had a sensitivity of 79% and specificity of 96% to detect stenoses of 50% or more reduction in the arterial lumen diameter.[61] Another study using similar parameters showed that the ABI had a sensitivity of 95% and a specificity of 100% compared with angiography.[62] Moreover, Feigelson et al measured a sensitivity and specificity of 89% and 99%.[63] The same study also reported a positive predictive value of 90%, and a negative predictive value of 99% with an overall accuracy of 98%. Despite the variation in reported

sensitivity values across different studies, the utility and overall accuracy of ABI measurements as a diagnostic tool for PAD has been well-established.

In a study by Ouriel and Zarins, the authors demonstrate that ABI may provide better discrimination than the absolute ankle pressure alone when comparing between normal lower limb arteries and those with PAD. However, neither ABI nor absolute ankle pressures can reliably differentiate between normal limbs and asymptomatic limbs that have arteriographically confirmed PAD. The authors explain that this may be because early stenotic changes can be mild and hemodynamically insignificant before becoming symptomatic.[64] This phenomenon is important when considering the utility of ABI in the postoperative surveillance of CLTI. McLafferty et al. conducted a study to determine if changes in the value of ABI correlated with progression of disease after open LER during a mean follow-up of 3.3 years. Using arteriography and DUS as standard, ABI had a sensitivity of 41%, specificity of 84%, positive predictive value of 59%, and an accuracy of 68% for detecting progression of disease.[65] Considering the cost-effectiveness and non-invasive nature of ABI measurements, these results suggest a role for ABI in monitoring disease progression after LER. Confirming the accuracy of abnormal ABI measurements with other imaging modalities such as DUS or arteriography would be reasonable.

It is important to note, that there are limitations to ABI measurements alone. Patients may have severely stenotic or totally occluded iliofemoral arteries yet exhibit a normal ABI at rest with adequate compensation from collaterals. Because the ABI relies on arteries being compressible for an accurate reading, extensive atherosclerosis rendering an artery non-compressible may artifactually increase the ABI value. Therefore, the presence of a normal or high ABI in patients with symptoms strongly suggesting arterial disease should receive additional testing to rule out CLTI. Alternative tests such as toe-brachial pressure, doppler

waveform analysis, pulse volume recording, exercise ABI test, or DUS may be used.[55] Saarinen et al compared patients monitored by ABI, toe pressures and DUS after EVT. ABI and toe pressures missed approximately 30% of lesions detected by DUS in post-EVT arteries.[23] The authors go on to explain how this discrepancy in lesion detection may cause unnecessary delay in repeat interventions for these patients. In fact, one study noted that a significant decrease in ABI, defined as >0.15 may not be present until a >60% stenosis exists.[48] This problem is particularly crucial in diabetic patients where ulcer healing time is longer and undetected stenosis may prolong that healing even more.

DUS utility in CLTI

DUS After Open Bypass:

A randomized controlled trial evaluated the effect of adding DUS to a surveillance protocol that included clinical examination and ABI after infrainguinal vein graft revascularization.[66] 179 patients undergoing infrainguinal vein graft revascularization during a 3-year period were scheduled for surveillance at 1, 3, 6, 9, and 12 months after operation. The authors compared the rate of reinterventions, overall cumulative assisted primary patency and secondary patency, and limb salvage. However, the study failed to show any beneficial effect of DUS in a surveillance program.

Lundell et al showed in an experimental study that patients who received a femoropopliteal graft had significantly better assisted-primary and secondary vein graft patency if they followed an intensive surveillance regimen as opposed to the routine surveillance protocol. The intensive surveillance regimen included clinical examination, ankle/brachial index measurements, and DUS scans every 3 months for the first 2 years, and yearly after operation. If

DUS scans showed stenosis, angiography was performed. If angiography showed stenosis, a revision (surgical or endovascular resulting in comparable outcomes) was performed. Routine surveillance was clinical examination and ankle/brachial index measurements without duplex scanning at 1, 12, 24, and 36 months after operation.[67] Angiography was performed for the routine surveillance group with recurrence of critical limb ischemia. Revisions were then performed based on angiography findings. This study suggested that the intensity of the surveillance program influenced outcomes, although it did not elaborate on compliance or the role of DUS.

DUS After EVT:

One analysis of routine DUS after infrainguinal EVT questioned the utility of post-EVT DUS surveillance.[24] Consecutive patients undergoing EVT of the superficial femoral artery (SFA) or popliteal artery were prospectively enrolled in a DUS protocol ≤1 week after intervention, then at 3, 6, and 12 months thereafter. The authors found that the natural history of arterial restenosis after EVT differs from that of vein graft bypass. The rate of thrombosis after EVT despite normal findings on initial DUS was significantly higher than that for vein grafts. After EVT, the tendency to develop restenosis was much greater, yet lesions appear more likely to stabilize or regress compared to those found in autogenous vein grafts. Finally, 82% of occlusions that occurred were in limbs in which only moderate, not severe, stenosis had been detected. The authors conclude that the sensitivity of post-EVT DUS to predict occlusion was 88%. However, the specificity was only 60%. An estimated 40% of the limbs showing restenosis on post-DUS EVT in this study would have gotten unnecessary interventions if DUS criteria alone were used.

A retrospective study conducted to evaluate whether DUS findings after infrainguinal endovascular interventions for critical limb ischemia (CLI) were predictive of need for reintervention or amputation over a period of 24 months.[25] DUS was performed within one month of the index procedure in 90 cases. 50 patients had an abnormal DUS result, and 40 patients had normal results. In patients with a normal duplex ultrasound the amputation rate was 5% vs 20% in the group with an abnormal duplex ($P = .04$). Primary patency was 56% in the normal duplex group and 46% in the abnormal duplex group ($P = .18$). Importantly, early DUS was able to identify residual stenosis not seen on completion angiography in 56% of cases. The authors report that an abnormal DUS in the first 30 days after an intervention is associated with an increased risk of amputation. They suggest a possible role for intraprocedural DUS, as well as routine postprocedural DUS and close clinical follow-up in patients treated for CLI. Spijkerboer et al conducted a study to determine if DUS one day after percutaneous transluminal angioplasty (PTA) is prognostic for hemodynamic and clinical results at one year.[26] 34 femoropopliteal artery segments treated with PTA received DUS imaging before PTA, one day after PTA, and one year after PTA. The authors then report that all three arterial segments which showed residual stenosis one day after PTA were occluded within one year. Clinical improvement was also seen in most patients with DUS improvement one day after PTA, whereas results of DUS at one year did not seem to correlate with hemodynamic or clinical status. Similarly, another study examining the utility of DUS surveillance of the tibial arteries after EVT reported that DUS surveillance did not significantly impact the outcomes of these patients.[52] Another study showed that the DUS criteria for restenosis of tibial arteries after prior EVT were reliable when compared to angiography. However, the authors mentioned that limbs with detected stenosis were only sent for repeat angiography if symptoms occurred.

The current guidelines support duplex ultrasound surveillance and prophylactic reintervention for asymptomatic vein graft stenosis to promote long-term patency. Guidelines for reintervention after EVT have been left up to the discretion of the operator. Reports from the literature vary in their thresholds for reintervention after EVT with most utilizing a mix of angiographic findings of restenosis and clinical symptoms to determine the choice. There is a paucity of high-grade evidence in the literature for the ideal indications for reintervention after EVT.[29] Hemodynamically significant restenosis as well as return of symptoms are the two main causes for reintervention gleaned from the literature review. As mentioned previously, however, the degree of restenosis required to observe clinical symptoms seems to vary. Regardless, it is reasonable to say that postoperative imaging is a key component for optimal follow up to detect disease before it becomes too severe.

A large study comparing the rate of postoperative imaging after LER between hospitals showed that nearly half of older patients in the United States do not receive any type of follow-up imaging after LER.[68] Indeed, the low rate of post-operative imaging was observed across the United States with no appreciable difference in imaging rates based on the modality of intervention, open versus endovascular. Therefore, despite the established guidelines for follow-up after LER with open surgery there still seems to be marked heterogeneity in the approach of physicians to this matter. These findings highlight the importance of establishing standardized and feasible guidelines for post-operative surveillance of CLTI. Furthermore, understanding the barriers that hinder physicians and patients from complying with a standardized post-operative imaging protocol is crucial.

A large retrospective study conducted by Wang et al recently reported that loss to follow-up at 1 year was associated with worse survival after open or endovascular LER for PAD.[21] The

aforementioned study supports the accepted belief that follow-up is critical to improving the long term outcomes of patients receiving LER, but does not offer data that would help determine a better follow-up regimen. Trials comparing surveillance frequency and modalities after EVT for CLTI are still needed. It is not clear why the findings of our study differed from those of Wang et al. One possible explanation is that our study utilized a different definition for follow-up compliance. Wang et al considered patients who received in-person or telehealth follow-up once during their first year post-operatively as compliant. Our definition of follow-up required in-person follow-up with a vascular specialist at a higher frequency. This also explains the much higher follow-up rate of 91% in the mentioned study compared to our rate of 61%. A study by Brooke et al reporting on in-person follow-up showed compliance rates closer to the ones we report.[68] In comparing outcomes of EVT and open bypass procedures for patients with CLTI, Iida et al. reported a 44% 3-year reintervention rate in a multicenter study of 452 CLTI patients who underwent revascularization by EVT or open surgery, comparable to the rates we observed in our study.[69] Moreover, our findings of factors associated with reintervention, major amputation, and mortality were consistent with those published in the literature.[70-73] It is possible that the higher reintervention rates of follow-up compliant patients could be related to overly aggressive reintervention thresholds. It is interesting to note that our regression analysis results showed that open/hybrid procedures were independently associated with lower chances of reintervention. Furthermore, the compliant with follow-up cohort had a significantly higher proportion of patients undergo open/hybrid procedures. Despite the seemingly protective role of the open/hybrid modality on reintervention rates, the compliant cohort still received a significantly higher reintervention rate, which would mean that compliant patients in the endovascular group must have received an exceedingly large number of reinterventions. Another

possible explanation for the difference in reintervention rate is self-selection. While there were

no appreciable differences in the perioperative outcomes recorded for the two cohorts, it remains

entirely possible that patients who had recurrence of symptoms were more likely to return to the

clinic and have more reinterventions.

The association of individual variables with follow-up non-compliance was not examined

in this study as there were no differences in the preoperative characteristics of patients. However,

efforts to improve patient outcomes and optimize follow-up schedules must highlight known

factors that influence patient outcomes and follow-up compliance. The study conducted by Wang

et al showed that those who were lost to follow-up had important demographic differences

including a higher proportion of nonwhite race, diabetes, and urgent presentations.[21] The

modality of follow-up also affected the long-term outcome of patients, with face-to-face follow-

up having a more protective effect against mortality compared to phone follow-up. Face-to-face

follow-up was also found to be protective against mortality in a study evaluating the impact of

follow-up on EVAR patients.[74] Patients who lived at home prior to admission showed lower

rates of loss to follow up than those who lived in nursing facilities, pointing to a possible adverse

effect of frailty on follow-up compliance.[75] Female patients were less likely to be lost to follow-

up, congruent with prior studies showing that males exhibited a higher no-show rate for

outpatient clinic appointments.[76] Urgent presentation has also been shown to be associated with

increased mortality in a large National Surgical Quality Improvement Program study.[78] Judelson

et al. conducted a study from a large national registry examining factors influencing loss to long-

term follow up after vascular procedures. Multivariable analysis showed that center-specific

attributes were highly influential in impacting loss to follow up status.[79] In fact, the authors note

that the effect size of the center was larger than the effects of all other factors combined. High

performing centers likely have specific processes in places to increase compliance with follow-up. The authors of this study quantified the lack of documented long-term follow-up in this large national registry and identified poor documentation as a key barrier to quality improvement. Future efforts at improving follow-up should focus on studying the documented processes of highly successful centers in follow-up compliance.

Guided by the review of literature conducted as well as the data gathered throughout this thesis, a few recommendations for follow-up can be made. Follow-up for CLTI should be decided based on the severity and anatomic location of the disease. All patients receiving LER for CLTI should be monitored by clinical visits including ABI and/or toe pressure measurements. A drop in the value of ABI of > 0.15 or recurrence of symptoms or change in pulse status should prompt further imaging. Patients with CLTI may receive EVT or bypass surgery to treat their disease. Due to the higher patency rates of revascularization in the aortoiliac segment, DUS imaging is likely to be beneficial in the immediate perioperative period and once in the first postoperative year if the patient remains asymptomatic. Patients who present with tissue loss have demonstrated significantly worse outcomes than those who present with rest pain.[80] Hence, patients with tissue loss due to infrainguinal disease should be monitored carefully after revascularization for tissue healing and be placed on a rigorous postoperative imaging surveillance regimen with DUS in the immediate perioperative period, 1 month, 3 months, 6 months, and 12 months postoperatively followed by every 6 months. Due to the results of the BASIL trial which revealed that CLTI patients receiving balloon angioplasty first for treatment of infrainguinal disease prior to bypass had worse survival, all patients receiving EVT for infrainguinal disease should be monitored with the same rigorous regimen described for tissue loss. There was no evidence in our study that would prompt a change in follow-up

recommendations for the societal guidelines of post-surgical bypass. The results of this study revealed that patients receiving open surgery had a lower likelihood of reintervention. Bypass surgery for patients with repeat occlusion after EVT may benefit this patient cohort more than repeat EVT, especially if an appropriate vein graft is available. Moreover, patients with risk factors such as end-stage renal disease, diabetes mellitus, and age > 75 years, should be carefully surveyed as these risk factors carry the highest risk of poor outcomes. Furthermore, patients with risk factors associated with loss to follow-up such as frailty, poor access to healthcare, or those who do not live at home should be counseled on options for transportation and methods to ease compliance with follow-up. Finally, any program of surveillance should carefully consider the cost of imaging, the burden of travel for patients, as well as the risk of unnecessary reintervention. Decisions to perform a reintervention on asymptomatic patients with recurrent stenosis in the treated segment should be approached cautiously and patients should be counseled appropriately on the consequences of restenosis and the risk of repeat occlusion.

The goal of treatment in CLTI is not only salvage of functional limbs, but also prevention of cardiovascular risk factors to improve mortality. Constant monitoring and evaluation of cardiovascular risk factors in all patients with CLTI is recommended by the Global Vascular Guidelines for management of CLTI.[29] Best medical therapy is critical and proven to improve outcomes of patients with CLTI. The long-term use of antiplatelets for all patients with CLTI is strongly recommended supported by high grade evidence coming from clinical trials showing improvement in mortality, myocardial infarction, and stroke.[81,82] While dual anti-platelet therapy is recommended over single agent use in some cardiovascular pathology, a meta-analysis that evaluating the use of ticagrelor, ticlopidine, aspirin, cilostazol, picotamide, vorapaxar, and clopidogrel as single antiplatelet therapy versus dual antiplatelet therapy in patients with PAD

found that clopidogrel monotherapy resulted in the best overall safety and efficacy.[83] Lipid-lowering agents, are also strongly recommended for all patients with CLTI, particularly those with high cholesterol blood concentrations. A Cochrane review evaluated 18 trials including 10,049 patients reported that analysis showed lipid-lowering therapy significantly reduced the risk of total cardiovascular events in PAD (OR, 0.74; CI, 0.55-0.98).[84] It is well established that control of blood pressure is crucial in the management of patients with cardiovascular disease. One study showed that PAD patients had a significantly higher incidence of mortality from cardiovascular events than those without PAD.[85] Furthermore, PAD patients were less likely to have cardiovascular events if their systolic blood pressure <145 mm Hg and diastolic pressures <90 mm Hg. Further reduction of blood pressure to below 130 mm Hg systolic and 80 mm Hg diastolic offered even greater protection from cardiovascular events. Therefore, control of hypertension is an essential component of medical management of CLTI patients. Diabetes is among the strongest risk factors for cardiovascular disease and PAD. Metformin is the first-line therapy used for management of type 2 diabetes mellitus. Patients requiring additional agents may be offered any of the other approved glucose lowering agents with equal effectiveness according to one study.[86] However, a large trial studying sodium-glucose co-transporter 2 (SGLT-2) inhibitors showed an approximate 2-fold increased risk of lower limb amputations associated with the use of canagliflozin, an SGLT-2 inhibitor.[87]

Lifestyle modifications are also critical components of management of cardiovascular disease, and CLTI patients may benefit greatly from adjustments such as smoking cessation, diet improvement, and exercise programs. The harmful effect of tobacco use on cardiovascular health is universally accepted. Patients who smoke should be encouraged to stop smoking at every clinical visit and should be referred to smoking cessation programs if they are still smoking. Diet

and exercise have not been specifically studied in CLTI. However, evidence in the literature

points to the benefit of healthy diet and exercise routines on progression of atherosclerotic

disease. Diets that reduce the intake of saturated fats and increases the intake of monounsaturated

fats, omega-3 fatty acids, antioxidants, and other natural plant sterols and stanols is associated

with a reduction in plaque burden and cardiovascular associated mortality.[88-90] Further, numerous

trials have demonstrated benefits of a gradual supervised exercise routine in intermittent

claudication.[91] Exercise rehabilitation has been shown to reduce the risk of recurrent myocardial

infarction and mortality.[92] Although no trials for exercise rehabilitation have been done on CLTI

patients, it is reasonable to assume benefits for this patient cohort. Lastly, pain is a significant

stressor in the lives of patients with CLTI. Ischemic pain in CLTI patients is often complicated

by coexisting neuropathic pain, especially in diabetic patients. No trials have been reported for

optimal pain management in CLTI. Global Vascular Guidelines recommends a tiered approach

to pain management, balancing the benefits and harms of pain medications. Patients should be

offered acetaminophen with additional opioids based on the severity of pain. Laxatives and

antinausea medications may be prescribed for those who develop gastrointestinal side-effects of

opioids.[29] Additional medications addressing neuropathic pain may also be prescribed in patients

already receiving high dose opioids with residual pain, especially in diabetic patients. These

medications include tricyclic anti-depressants, gabapentin, and pregabalin. However, care should

be taken to the associated cardiac risks of such medications.

Limitations:

Finally, this study has several limitations related to its retrospective design. The chart of

any patient that was found to be non-compliant with follow-up was carefully reviewed for any

evidence of follow-up visits with an outside provider by reviewing notes in the chart that may

indicate outside follow-up. It is impossible to know with certainty whether some patients

followed with a vascular provider outside the system but kept follow up for other medical needs

within the system. That can potentially be captured as lack of compliance with the vascular

provider through the EMR review. However, this scenario should be limited to a very small

minority of the patients. Furthermore, the definition used in this study for compliance constitutes

the minimal recommended regimen of follow-up for a group of patients with predominantly

tissue loss. In practice, these patients require multiple visits during the first 1-2 months to ensure

wound healing, absence of infection and adequate revascularization. It is unclear whether an

alternative definition of compliance with a different frequency of follow up visits would have

affected the results of this study. During chart review, patients were recorded as compliant or

non-compliant based on the criteria of the study. The date of every individual visit which would

qualify as a clinical follow-up visit was not recorded nor were details of what occurred during

this follow-up. Testing of the impact of different follow-up schedules may have been possible if

these dates were recorded and would be a helpful element to consider in future studies of this

topic. Furthermore, self-selection bias from patients with recurrent symptoms may have

influenced the results of this study. Future studies examining the role of follow-up should

emphasize the clinical status of patients at each follow-up visit to control for this possible

confounder. Moreover, the lack of information regarding surveillance methods used during

follow-up visits prevents the passing of any judgment on the quality of follow-up for every

individual patient. Differences in post-operative adherence to best medical management,

smoking cessation, and proper wound care were not assessed in this study and could have

significantly impacted patients' outcomes. Also, different thresholds for reintervention among

different providers in the same specialty or across the various disciplines could have introduced selection bias in some groups of patients and affected our results.

5. Conclusion

Compliant patients with follow up after LER for CLTI had higher reintervention compared to non-compliant patients. However, there was no difference between the 2 groups in major amputation or mortality. Prospective trials to define the optimal modalities of surveillance, follow up frequency, and thresholds for reintervention after LER are needed.

Table I: Characteristics of compliant and non-compliant patients with CLTI undergoing lower

extremity revascularization

Characteristics	Non-Compliant (N=138) N(%)	Compliant (N=218) N(%)	P
Demographics			
Age (mean ± SD)	69.8 ± 11.5	68.8 ± 12.8	0.467
Male	89 (64.5)	125 (57.3)	0.179
Smoking Status			0.062
Former	53 (38.7)	109 (50)	
Current	35 (25.6)	54 (24.8)	
Nonsmoker	49 (35.8)	55 (25.2)	
Race			0.952
White	93 (68.4)	146 (67.9)	
African American	28 (20.6)	43 (20.0)	
Other	15 (11.0)	26 (12.1)	
Body Mass Index (Mean ± SD)	29.6 ± 6.6	28.3 ± 6.8	0.081

Comorbidities			
Diabetes	95 (68.8)	142 (65.14)	0.471
Chronic renal insufficiency	38 (27.5)	48 (22.1)	0.246
End Stage Renal Disease	13 (9.4)	32 (14.7)	0.146
Hypertension	122 (88.4)	190 (87.2)	0.727
Hyperlipidemia	88 (63.8)	126 (57.8)	0.262
Coronary artery disease	57 (41.6)	105 (48.0)	0.199
Congestive heart failure	32 (22.9)	38 (17.4)	0.199
Stroke	21 (15.0)	22 (10.1)	0.159
Hypercoagulable disorder	2 (1.4)	0	0.153
History of cancer	20 (14.3)	35 (16.0)	0.663
Prior endovascular intervention	17 (12.1)	35 (16.0)	0.313
Prior open surgery	15 (10.7)	32 (14.6)	0.286
Serum creatinine	1.6 ± 1.9	1.7 ± 1.9	0.944
Medications			

Aspirin	84 (60.9)	142 (65.7)	0.352
ADP receptor/P2Y12 inhibitor	46 (33.3)	61 (28.0)	0.283
Anticoagulant	22 (16.0)	45 (20.6)	0.269
Statins	87 (63.0)	144 (66.4)	0.523

SD, standard deviation;

Table II: Procedural characteristics of lower extremity revascularization in compliant and non-compliant patients with CLTI.

Procedures	Non-compliant (N=138) N(%)	Compliant (N=218) N(%)	P
Indication			0.180
Rest Pain	19 (13.8)	42 (19.3)	
Tissue Loss	119 (86.2)	176 (80.7)	
Procedure Type			0.003*
Endovascular	128 (92.8)	173 (79.4)	
Open	8 (5.8)	37 (17)	
Hybrid	2 (1.5)	8 (3.7)	
Endovascular treatment			0.430
PTA	61 (47.3)	91 (50.3)	
Stent	41 (31.8)	63 (34.8)	
Atherectomy	21 (16.3)	18 (9.9)	
Atherectomy/Stent	6 (4.7)	9 (5)	
Endovascular anatomical location			0.051
Aortoiliac	7 (5.4)	27 (15)	
Femoro-popliteal	42 (32.6)	56 (31.1)	
Tibial	45 (34.9)	49 (27.2)	
Multi-level	35 (27.1)	48 (26.7)	

Open Surgery			
Suprainguinal bypass	1 (0.72)	8 (3.7)	0.085
Axillary to femoral bypass	1 (100)	4 (50)	
Aorta/iliac artery bypass	0	4 (50)	
Infrainguinal bypass	8 (5.8)	29 (13.3)	0.024*
Common femoral endarterectomy	3 (2.2)	19 (8.7)	0.013*

PTA, Percutaneous transluminal angioplasty.

*statistically significant

Table III: Perioperative outcomes of compliant and non-compliant patients with CLTI

undergoing lower extremity revascularization

Short-term Outcomes (30 days)	Non-Compliant (N=138) N(%)	Compliant (N=218) N(%)	P
Hematoma	3 (2.3)	4 (1.9)	1.000
Pseudoaneurysm	2 (1.5)	1 (0.46)	0.561
Bleeding	10 (7.5)	19 (8.8)	0.665
Wound infection	7 (5.3)	19 (8.8)	0.222
Pneumonia	2 (1.5)	1 (0.46)	0.560
Urinary tract infection	1 (0.76)	3 (1.4)	1.000
Arterial Thrombosis	2 (1.5)	2 (0.93)	0.639
Deep venous thrombosis	3 (2.3)	5 (2.3)	1.000
Stroke	0	1 (0.46)	1.000
Acute renal failure	8 (6)	11 (5.1)	0.809
Acute/new HD requirement	1 (0.75)	4 (1.85)	0.653
Return to Operating room	14 (10.6)	36 (16.7)	0.118
Major amputation	5 (3.8)	8 (3.7)	1.000
Any morbidity	32 (23.2)	58 (26.6)	0.470
Mortality	2 (1.5)	0	0.146

HD, hemodialysis

Table IV: Long-term Outcomes of compliant and non-compliant patients with CLTI undergoing

revascularization

Long-term Outcomes	Non-Compliant (N=138) N(%)	Compliant (N=218) N(%)	P
Follow-up time (mean in years ± SD)	2.8 ± 2.0	2.6 ± 1.6	0.202
Ipsilateral reintervention rate	47 (34.1)	107 (49.1)	0.005*
Number of ipsilateral reinterventions (mean ± SD)	1.6 ± 1.1	2.2 ± 1.8	0.020*
Ipsilateral Reintervention Index. (Ipsilateral reintervention/year of follow-up)	1.1 ± 2.7	1.5 ± 2.0	0.419
Reintervention rate (any leg)	61 (44.2)	133 (61.0)	0.002*
Number of reinterventions (any leg) (mean ± SD)	2.1 ± 1.7	2.7 ± 2.3	0.036*
Reintervention Index (All reinterventions/years of follow-up)	1.2 ± 2.4	1.8 ± 2.2	0.094
Ipsilateral Major Amputation	16 (11.6)	40 (18.4)	0.088
Mortality	55 (39.9)	74 (33.9)	0.258

*statistically significant

Table V: Multivariable regression analysis of independent factors associated with ipsilateral reintervention, major amputation, and mortality:

Variable	Ipsilateral reintervention OR [95% CI]	Major Amputation OR [95% CI]	Mortality OR [95% CI]
Smoking			
Former	0.77 [0.45, 1.31]	0.61 [0.30, 1.25]	1.03 [0.59, 1.81]
Current	1.47 [0.78, 2.77]	0.70 [0.31, 1.61]	1.44 [0.72, 2.90]
Age	0.98 [0.96, 1.00]*	0.99 [0.96, 1.02]	1.05 [1.02, 1.07]*
Body Mass Index	0.97 [0.94, 1.01]	1.00 [0.95, 1.05]	0.99 [0.95, 1.03]
Compliance with follow-up	1.82 [1.15, 2.89]*	1.56 [0.81, 3.00]	0.72 [0.44, 1.16]
Diabetes	0.80 [0.49, 1.33]	0.89 [0.44, 1.78]	0.95 [0.63, 1.83]
End stage renal disease	1.29 [0.66, 2.52]	4.16 [1.95, 8.86]*	4.88 [2.38, 10.01]*
Coronary artery disease	1.08 [0.69, 1.70]	1.00 [0.54, 1.85]	0.65 [0.85, 2.22]
Congestive heart failure	1.17 [0.65, 2.11]	0.36 [0.14, 0.95]*	0.65 [0.83, 2.79]
Procedure Type (Open/hybrid)	0.48 [0.27, 0.83]*	2.59 [1.17, 5.77]*	1.38 [0.68, 2.79]

*statistically significant

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