Severe Peripheral Artery Disease: New Observations from a Community-Based Minnesota Registry

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Abstract

This study assessed whether time serves as a previously undefined predictor of both limb and patient survival in individuals with acute limb ischemia (ALI) and critical limb ischemia (CLI). Patients with ALI or CLI referred to a single metropolitan tertiary care hospital were consecutively entered into the prospective "FReedom from Ischemic Events: New Dimensions for Survival" (FRIENDS) registry. Demographics, key time segments and short-term outcomes were evaluated for all patients. Key time segments were reported as median and interquartile range (IQR). Myocardial infarction (MI), stroke, amputation and all-cause mortality were collected at one month. From 2/07 through 12/09, 206 patients (75 ALI, 131 CLI) were enrolled in the FRIENDS registry. The median age was 76 (64, 84) years and 58% were male patients. Median time from symptom onset to admission was 19.2 hours (7.2, 79.2) for ALI and 59 days (24, 124) for CLI patients. Length of stay was 7.0 days (4.3, 10.4) for ALI and 6.1 days (3.1, 10.7) for CLI patients. Minor and major amputation was performed during the index hospitalization in 10 (13%) of patients with ALI and 34 (26%) of those with CLI. In ALI patients, amputation was significantly associated with increased duration of ischemia (P=0.015 for trend), but this trend was not observed in CLI patients. One month after discharge, a longer duration of ischemia was significantly associated with an increase in the quadruple endpoint of nonfatal MI, stroke, amputation or death in patients with ALI (P=0.007 for trend). No such association was observed in individuals with CLI. Amputation-free survival at one month was 78.7% and 71.8% for patients with ALI and CLI, respectively. In conclusion, these data suggest that expedited admission and treatment for ALI is associated with lower rates of in-hospital amputation and morbidity and mortality at one month. There was no association between the duration of ischemia and morbidity and mortality among the CLI patients. These data clarify a high incidence of ALI amongst patients with severe PAD; verify that length of stay remains long and major adverse outcomes remain common even within the first month of a severe PAD admission. Future research might investigate the biological mechanisms and processes of care that could link the long referral times and high rates of vascular ischemic events.

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1. INTRODUCTION

Acute limb ischemia (ALI) and chronic critical limb ischemia (CLI) are defined as the clinical syndromes caused by the most severe compromise of blood flow to the affected lower extremity. This severe decrease in leg perfusion is associated with the development of ischemic leg pain that occurs at rest and with non-healing wounds, and is associated with impending limb loss. The term CLI is defined by most vascular specialists as the most severe clinical manifestation of peripheral artery disease (PAD) in which major limb amputation would be likely to occur within 6 months without reestablishment of adequate leg blood flow.[1] ALI is defined by the sudden complete occlusion of a major leg artery that is usually manifested as an acutely cold, pale or blue extremity. For such individuals amputation may occur within a very short time frame (hours to days) and the mandate to re-establish limb blood flow is a medical emergency.[2]

Individuals with ALI and CLI represent a population that bears a large systemic atherosclerotic burden. Critical limb ischemia is associated with a very high 6-month morbidity and mortality. Patients with the most minimal clinical manifestations of atherosclerotic lower extremity PAD (including the absence of any recognized leg ischemic symptoms) have a 3 to 5-fold greater risk of cardiovascular mortality than those without PAD (including a minimum 3-5% annual rate of myocardial infarction (MI), stroke, or death, and 25-30% annual rate of MI, stroke, hospitalization, or death). Individuals with ALI or CLI face an even higher 25% one year mortality, and less than 50% annual rate of amputation-free survival.[3-6]

It is generally accepted that hypoperfusion of the leg leads to irreversible ischemia when revascularization to restore adequate distal blood flow is not accomplished in a timely manner. Regardless of treatment modality used, it is presumed (in the absence of any prospective clinical evidence) that efforts to minimize the duration of ischemia and reduce diagnostic and treatment delays would decrease the risk of amputation and potentially reduce cardiovascular adverse outcomes.

Thus, care strategies for individuals with both ALI and CLI must accomplish: (a) prompt diagnosis of the PAD etiology when individuals suffer these severe manifestations of PAD; (b) prompt referral of such individuals to vascular specialty care; (c) immediate re-establishment of leg perfusion, for individuals with viable limbs, by either endovascular or surgical techniques; and (d) establishment and continuation of treatment of the systemic atherosclerotic risk in order to minimize rates of heart attack, stroke and death.

In 2005, the first interdisciplinary "ACC/AHA Guidelines for the Management of Peripheral Arterial Disease"[5] was published, and included both ALI and CLI clinical care recommendations and care algorithms. Soon thereafter, an update of the international TransAtlantic Inter-Society Consensus (TASCII) for the Management of Peripheral Artery Disease was published in 2007 emphasizing early referral in the course of CLI to a vascular specialist to plan revascularization options.[6]

Yet, to our knowledge, no health system-based ALI/CLI care pathway has ever been created in order to facilitate delivery of these recommendations, extending from primary care identification of ALI/CLI, transfer for urgent revascularization, and provision of guideline-based long-term risk reduction.

2. REVIEW OF THE LITERATURE

2.1. Acute Limb Ischemia

Acute lower extremity ischemia is well recognized as a vascular emergency presentation of PAD and is a cause of considerable morbidity and mortality. According to the TASC II 2007 guidelines,[6] ALI is defined as a sudden decrease in limb perfusion that causes a potential threat to limb viability in patients who present within two weeks of the onset of acute symptoms. Patients with similar manifestations who present later than two weeks are considered to have critical limb ischemia, which is by exclusion then defined as “chronic”. The rationale for use of the two week time frame for this definition of ALI has never been based, to our knowledge, on an evidence base presented in the published literature. Specifically, there is no obvious pathophysiological mechanism that could underlie this arbitrary diagnostic time-based syndrome definition.

Limited contemporary population-based data are available to accurately estimate the incidence or prevalence of ALI. An audit carried out in Gloucestershire/UK and published in 1997, in a population of 540,000, reported 77 cases of ALI, using the standard clinical definition.[7] The annual incidence was thus estimated to be 140 per million de novo native artery cases per year, and this rate increased to 170 per million per year if post-surgical bypass graft occlusions were included.[7] The Swedish Vascular Registry confirmed these general rates, reporting an estimated incidence of 130 ALI cases per million per year.[8] Men and women were equally at risk in these studies.[9] It is hypothesized that the incidence of ALI will become more frequent as the population ages[10], and as atherosclerotic PAD, atrial fibrillation, heart failure, and other ALI-related co-morbid pre-conditions increase. This projected increase will undoubtedly stress national the health care budgets if there are no health care system care pathways in place to cost-effectively prevent or treat this problem.

ALI is a clinical syndrome, and not a single pathophysiologically-defined disease. ALI may occur as the result of embolization from a cardiac or more proximal arterial source, or be due to in-situ thrombosis of a native artery or bypass graft occlusion. Bypass graft occlusions generally occur in response to a reduction in graft flow from a stenotic lesion within the conduit, compromised outflow, or reduced inflow. In prosthetic grafts, however, thrombosis may develop in the absence of a causative anatomic lesion.[11] However, the two main causes of ALI are embolism and thrombosis, accounting for approximately 78% of the cases.[12] Differentiation between these two etiologies can be difficult (such as via use of a clinical history or angiographic visualization of the occlusion), and is clinically impossible in 10–15% of cases.[13] With the increased use of peripheral arterial bypass grafts as a treatment for PAD (including presentations of acute and chronic critical limb ischemia), and noting the finite time-dependent patency rate of any bypass graft conduit, acute graft occlusion thus logically is an increasingly frequent cause of ALI as well.[14]

Irrespective of the etiology of ischemia, sudden hypoperfusion of the distal extremity results in clinical signs and symptoms of profound ischemia. Patients complain of numbness and pain in the extremity that may rapidly progress to motor loss and muscle rigidity. The "5 Ps" have been used as a mnemonic to remember the key presentation hallmarks of ALI: *p*ulselessness, *p*allor, *p*ain, *p*aresthesia (numbness), and *p*aralysis. In some textbook definitions, a sixth P for *p*oikilothermia is added, meaning coolness.[6] The ischemia in the lower extremity leads to a conversion of muscle metabolism from aerobic to anaerobic pathways, resulting in an increase of lactate concentration and acidosis. The result of prolonged severe leg ischemia is the build-up of toxic byproducts within the ischemic tissue bed resulting in skeletal muscle fiber necrosis and ischemia-induced leakage of protein and fluid from the capillary bed, thus producing tissue edema.[15-16] This process, amplified by reperfusion, occurs at a microscopic level, but may progress to the development of a compartment syndrome.[16]

In general, it is believed that prompt treatment is the most important factor in successful efforts to save a threatened, but viable, leg. Despite advances in surgical skills and techniques (such as the rapid evolution and use of endovascular revascularization techniques), ALI continues to be associated with substantial rates of limb loss and considerable mortality. Large series have reported 30-day mortality rates of approximately 15%, and 30-day amputation rates of approximately 10% to 30%.[13] In a retrospective study of 80 patients with ALI due to acute thrombosis and 192 due to embolism, the 5-year mortality was 56% and 83%, respectively, suggesting that ALI is a fatal disease.[2] One of the important risk factors determining the limb outcome of patients with ALI is the duration of leg ischemia. A series of 400 peripheral arterial embolectomies performed in 326 patients over a 34-year period demonstrated that in-hospital major amputation increased with increasing time delay from onset of ischemia to the time of arterial embolectomy.[17] Amputation rates were 6% for embolectomies performed within 12 hours of onset of ischemia, 12% when performed within 13 to 24 hours and 20% when performed after 24 hours of onset of ischemia.[17] A more recent study confirmed this relation, demonstrating that duration of ischemia may be a crucial risk factor predicting limb outcome.[18] Thus, it would be logical for a health care system to create a clinical care pathway in order to facilitate identification of ALI, and transfer of patients for immediate revascularization. By shortening these time segments, one might hypothesize that it would be possible to observe a decrease in amputation rates.

2.2. Critical Limb Ischemia

Critical limb ischemia also represents a manifestation of severe PAD and ischemic amputation is its most devastating limb outcome. Thus, both CLI and ischemic amputation remain a large problem in the United States in terms of morbidity, mortality and cost. CLI is the term used to describe the chronic severe decrease in lower extremity arterial perfusion that is insufficient to meet the metabolic requirements to sustain tissue viability. The clinical definition of CLI includes ischemic pain at rest, skin ulceration or frank gangrene for more than two weeks.[19] As noted previously, the pathophysiologic rationale (or natural history data) that would underpin use of a two week ischemic symptoms “cutpoint” to distinguish ALI from CLI is unclear. The two most popular systems for classifying PAD are the Fontaine stages (mostly used in Europe) and Rutherford categories (mostly used in the USA). Both the ACC-AHA Guidelines for the Management of Patients with PAD[5] and the TASC 2007 guidelines[6] classify CLI as Fontaine stage III for ischemic rest pain and stage IV for ulcer or gangrene, whereas Rutherford categories apply “4” for ischemic rest pain, “5” for minor tissue loss and “6” for major tissue loss.

It has been estimated in the UK that there are approximately 20,000 people with CLI in the general population, with annual incidence of 400 per million per year.[20] The Oxford Vascular Study[21] followed up 19,100 subjects to record non-coronary events and found that the incidence rate for CLI was 0.34 per 1000 population per year. Extrapolation from the better-documented prevalence studies of intermittent claudication (IC) has been performed to yield an approximation of the incidence of CLI. If one assumes that the overall population prevalence of IC is 3% and that patients with IC will develop CLI at a 1-3% annual rate[19] then the incidence of CLI would be estimated at 300 to 900 per million per year. This projected CLI annual incidence is a conservative approximation and may underestimate the true incidence, as it is also known that CLI may occur *de novo* in individuals with asymptomatic PAD as well as in individuals with atypical leg pain.[22] However, interpretation of these data should be performed cautiously as the calculation is based on extrapolation from different population samples. Another approach that has been used to estimate CLI prevalence has related "clinical CLI" as a denominator derived from the known incidence of amputation. These calculations assume that most amputations are due to CLI and that 25% of patients with CLI will require amputation. Thus, the incidence of CLI would be estimated to be between 500-1000 per million per year.[19] More recently, Jensen et al[23] used a questionnaire to estimate the prevalence of CLI in a population of 20,300 Norwegians aged 40-69 years. The authors defined CLI as ischemic rest pain or ulcers affecting the toes, foot or ankle that have failed to heal. They found that the prevalence of CLI was 0.26% among men and 0.24% among women.[23] They also observed that the prevalence of CLI increased with age for both sexes and the rates were highest in the 60-69 year age group.[23] Major risk factors for development of CLI include age, current smoking, hypercholesterolemia, an ankle-brachial index below 0.7, and diabetes.[19] As the population survives longer with chronic cardiovascular diseases, and experiences increased obesity and diabetes (both potent risk factors for atherosclerosis), it is assumed that the prevalence of CLI and ischemic amputation will increase, resulting in a growing clinical and economic burden for national health care systems.

The delivery of clinical care for PAD, including individuals with ALI, CLI and ischemic amputation, is associated with substantial health care expenditure in the Medicare population. In the U.S., a total of $4.37 billion was spent in 2001 only on PAD-related treatment (excluding the costs of associated MI and stroke) and 88% of expenditures were for inpatient care.[24] The high economic burden of PAD has been further elucidated in a one-year prospective cost analysis associated with atherothrombosis-related clinical events and procedures in the international REduction of Atherothrombosis for Continued Health (REACH) registry; in this setting, the authors concluded from 2004 U.S. census data, total annual costs would be $21 billion.[25] Allie et al[26] estimated a total average cost of $32,000 per CLI patient over a period of 18 months. The University of Minnesota vascular research group recently estimated the age-adjusted annual incidence of ischemic amputation (minor and major amputation) in Minnesota to be 21.2 cases per 100,000 with associated acute care hospital charges of $31,900 per patient.[27] This Minnesota data would be extrapolated to a total national healthcare cost of $3.1 billion for ischemic amputation care alone (excluding rehabilitative interventions) when applied to the 2008 U.S. population.[27]

Patients with CLI face a dismal prognosis in terms of both survival and limb preservation. The primary amputation rate varies between 10 and 40% within a year after a first diagnosis of CLI.[19] Patients with CLI suffer a high mortality rate, because atherosclerotic disease is established in various arterial beds (e.g., brain and heart) at the time of the CLI diagnosis.[28] The prognosis is comparable to that of some malignant forms of cancer.[1] Overall, one and five-year mortality rates of patients with CLI are reported to be 20-25% and 40-70%, respectively.[29-31]

It is well recognized that patients with CLI suffer diagnostic delays and poor achievement of atherosclerosis risk factor goals, which likely contribute to limb loss, non-fatal cardiovascular ischemic events, and poor patient survival. The current standard of care for CLI relies on direct revascularization, either by endovascular techniques or open surgical approaches. However, unlike myocardial infarction or stroke, CLI seems not to be well-recognized by cardiovascular clinicians as a “vascular emergency” and has not been the traditional focus of care for either primary care physicians or most non-vascular surgical cardiovascular clinicians. Although national and international PAD care guidelines define evidence-based care pathways, these guidelines do not yet trigger a uniform algorithm of care. Patients with CLI should undergo an expedited vascular assessment and a high percentage should be recommended to undergo prompt revascularization to avoid amputation. Despite this recommendation, single center case series suggest that patients with CLI still suffer major diagnostic delays[32-33] and poor atherosclerosis risk factor control.[34-36] An analysis of the Medicare reimbursement claims data suggest that a significant 67% of patients with CLI in the US elderly population were treated with primary amputation and of those only 51% had an ankle-brachial index

(ABI) measurement or angiography prior to amputation.[26] Thus, a defined health care pathway delivering systematic care could be implemented in hospitals in order to facilitate identification of CLI, transfer for expedited revascularization, and provision of guideline-based long-term risk reduction.

3. STUDY OBJECTIVES

The goals of the Acute Limb Ischemia/Critical Limb Ischemia Program are:

- To describe the first health care pathway to facilitate identification of ALI/CLI and transfer for expedited treatment;
- To define the contemporary fraction of ALI and CLI cases in a severe PAD population;
- To determine the atherosclerosis risk factors and co-morbidities of individuals with ALI/CLI in a community-derived Minnesota population;
- To evaluate use of evidence-based risk reduction medication on admission and discharge
- To assess ambulatory status at baseline and improvement at discharge and 30 days;
- To describe the 30-day amputation-free survival of individuals with ALI/CLI and 30-day rates of heart attack, stroke, amputation and death;
- To evaluate the association between the onset of clinical symptoms of ALI/CLI, time to diagnosis, and time to re-establishment of limb perfusion on these clinical outcomes.
- To provide pilot data to support an NHLBI application to perform a cluster randomized interventional trial of this care pathway to decrease the population-based incidence of amputation in ALI/CLI patients

Our primary hypothesis was that (a) control of cardiovascular risk factors is insufficient in patients with ALI/CLI as compared to recommended guidelines, and (b) that the time from symptom onset to revascularization serves as a previously undefined predictor of both limb survival and patient survival.

4. METHODS

4.1 Study Design

The study design is that of a prospective registry of individuals with severe PAD who presented for care in a large metropolitan vascular center, providing direct assessment of care during the index hospitalization. Telephone follow-up was conducted at 1, 6 and 12 months after initial hospitalization.

4.2 Definition of ALI/CLI

Acute limb ischemia (ALI) was clinically defined by the admitting vascular specialist as any sudden decrease in limb perfusion causing a potential threat to limb viability of less than or equal to two weeks in duration. Critical limb ischemia (CLI) was defined as Rutherford classes 4, 5 or 6 (presence of symptoms for more than two weeks with ischemic rest pain, minor or major tissue loss). An objective definition, such as via use of pedal or toe pressure, was not required for study entry.

4.3 Creation of a Health Care Pathway

In the electronic medical record system (Epic®, Verona, WI), an admission and discharge order set for patients with ALI/CLI was created (Appendix 1-2). Standardized transfer orders were also created to facilitate transfer of ALI/CLI patients to the vascular center (Appendix 3). Admission of ALI or CLI patients via use of the electronic medical record orders triggered automated delivery of the patient name to an electronic research folder announcing admission of the patient to the research staff (HK). Use of this electronic record system facilitated both the initial identification and subsequent tracking of all severe PAD patients and thus consecutive enrollment was ensured. An acute admission/vascular consultation dictation template was provided to the vascular specialty staff to ensure that all necessary data fields were sought from the patient and then immediately dictated into the admission consultation, and thus served as one reliable source document (Appendix 4). An ALI/CLI treatment algorithm was created in pocket size format and was distributed to all vascular specialty medical staff and emergency room medical staff as a template to facilitate delivery of a standardized systematic care plan (Appendix 5). An ALI/CLI-specific written health care plan, with inclusion of the need to sustain care for the ischemic limb and to decrease cardiovascular risk was provided to each ALI/CLI patient, or a family member, at hospital discharge to improve patient and leg survival (Appendix 6).

4.4 Patient Selection and Data Abstraction

All eligible patients with ALI or CLI referred to a single metropolitan tertiary vascular care center were consecutively entered into the prospective "FReedom from Ischemic Events: New Dimensions for Survival" (FRIENDS) registry. Medical record documentation was required for establishment of the presence of ALI or CLI. Vascular specialty staff received instruction on: (a) the clinical definitions of ALI and CLI as reviewed above; (b) how to create a source document on patient admission that included the time of onset of symptoms; and the benefit of utilizing measurement of pedal or great toe pressures to objectively establish the severe PAD (ALI or CLI) diagnosis.

Documented CAD consisted of 1 or more of any following chart documented conditions: stable angina, previous myocardial infarction, history of percutaneous coronary intervention or history of coronary artery bypass graft surgery. Documented CVD consisted of a history of transient ischemic attack (TIA), history of ischemic or hemorrhagic stroke, history of carotid stenting or carotid endarterectomy. Documented PAD consisted of 1 or more of the following criteria: symptomatic PAD defined by history of claudication, asymptomatic PAD documented in the medical records, or past history of ALI or CLI.

Baseline height and weight were obtained from the medical records. From these data, body mass index (BMI) was calculated using weight in kilograms divided by the square of height in meters. Patients were considered to be overweight if they had a BMI of 25 kg/m^2 to less than 30 kg/m^2 or obese if they had a BMI of 30 kg/m^2 or higher. Atherosclerosis risk factors were considered to be present if these were documented in the medical record or if patients were receiving treatment for the risk factor at the time of study enrollment. Diabetes was considered present when chart documented regardless of type (I or II), or use of antidiabetic medication (or dietary intervention). Also, fasting blood sugar greater than 7 mmol/l or 126 mg/dl was considered evidence of diabetes when this laboratory data were available. Hypertension consisted of chart documentation of hypertension or treatment with any antihypertensive medication or behavioral intervention (e.g., calcium channel blockers, ACE-inhibitors, beta blockers, diuretics or diet/exercise). Dyslipidemia was considered present when there was chart documentation of dyslipidemia or use of any lipid-lowering or cholesterol modifying medication (e.g., statin, niacin, fibrates, or bile acid binding resin agents). Dyslipidemia was also considered to be present if, per the National Cholesterol Education Program guidelines, the total cholesterol concentration was >200 mg/dl (5.18 mmol/l), LDL concentration was > 130 mg/dl (3.37 mmol/l), or HDL concentration less than 40 mg/dl (1.04 mmol/l). Other criteria for establishment of dyslipidemia included a triglyceride concentration of 200 mg/dl, or total cholesterol/HDL ratio of 5.0 or more. Smoking history was recorded as "current" if cigarettes were used within one month of encounter, "former" if smoking had stopped more than one month prior to this encounter; and "never" if there was no prior history of cigarette use. A family history of premature CAD consisted of any chart documentation of a family history of premature CAD or any myocardial infarction (MI) in a first-degree relatives, male <55 years and female <65 years. The etiology of ALI was coded from what was documented in the medical records.

Ambulatory status on admission and discharge was collected by self-report or abstracted from the report of the physiotherapists in the hospital. Ambulatory status was stratified into five categories and assigned values of 1 to 5 for each category, with 5 representing the best ambulatory status and 1 the lowest ambulatory status. Five was assigned to “full ambulatory”, defined as the ability to independently ambulate and fully interact in the community. “Minimal ambulation” was defined by ambulation limited to within the house/hospital, around the house/hospital and to the mail box and was assigned a value of 4. “Ambulation with assistance” was defined by ambulation needing another person’s help for mobility and was assigned a value of 3. “Wheelchair bound” was defined by dependency on a wheelchair for mobility and was assigned a value of 2. “Bed bound” was defined when the patient was not mobile at all and was fully restricted, and non-ambulatory and was assigned a value of 1. Functional status at baseline was assessed as the level of function after onset of severe PAD and within one week before admission.

All data were collected via use of a standardized case report form and then entered into a password-protected Access® database. The study was approved by the institutional review board at Allina Health Systems for performance at Abbott Northwestern Hospital, Minneapolis, Minnesota.

4.5 Key Time Segments

The symptom onset of initial ALI/CLI was defined by the patient’s description provided to the vascular specialist at the first hospital encounter, was dictated into the encounter note, and this note (date and time) was abstracted from the medical records. Vascular specialty staff were instructed to document the precision of date and time interval of limb symptom onset within an hour for patients presenting within 3 days, within a day for patients presenting within 3 to 30 days, and within a week for patients presenting with more than one month symptom onset. For CLI patients that could not state an exact time of leg symptom onset, we assumed that the onset time was 12 noon on the day specified. The “admission to ABI” time segment was defined as the time from admission to initiation of the first hospital-based ABI, toe-brachial index or transcutaneous oxygen pressure measurement. The “admission to heparin” time was defined as the time from admission to the initiation of a therapeutic intravenous heparin infusion. The “admission to vascular specialist at bedside” time segment was defined as the time from admission until the patient was evaluated by a vascular specialist, and this was set by the time of the dictated note. The "admission to treatment" time segment was defined as the time from admission until the patient was in the operating room or catheterization laboratory, and included only the use of an endovascular procedure, surgical procedure or primary amputation (medical treatment alone was not included in this definition). Hospital length of stay was defined as the number of days of hospitalization from admission to discharge. All time segments were analyzed for ALI patients as all cases were hospitalized on an emergent basis. Unlike ALI, CLI patients were not uniformly hospitalized on an emergent basis. Thus the time segments from admission to any treatment in the hospital do not apply. We therefore, calculated the time segment from "symptom onset to admission" and time segment from "symptom onset to treatment".

4.6 Primary Outcome Measures

The primary outcomes of interest were nonfatal MI, nonfatal stroke, all amputation, major amputation, all-cause death, rehospitalization for cardiovascular (CV) events, rehospitalization for non CV events, ALI/CLI recurrence and the composite triple endpoint (defined as any nonfatal MI, stroke or amputation) and the quadruple endpoint (defined as any non-fatal MI, stroke, amputation and death). "Minor amputation" was defined as removal of part of the lower limb below the ankle and "major amputation" was defined as removal of part of the lower limb above the ankle. All-cause mortality was ascertained via the social security death index website[37] using the social security number, name and birthdates to identify cases. Additional systemic and limb outcome events included TIA, unstable angina, worsening of PAD (but not new ALI or CLI), chronic heart failure (CHF), any other ischemic arterial event, or bleeding leading to both hospitalization and transfusion.

Follow-up phone calls were performed at 1 month ±1 week, 6 months ±1 month and 12 ±2 months after hospital discharge using a phone script containing standardized questionnaires. The occurrence of non-fatal MI, non-fatal stroke, amputation, or death, and functional status were ascertained by self-report during follow-up calls. Incident cases of MI, stroke or amputation were ascertained by medical records. There was no independent clinical events committee to adjudicate events.

4.7 Statistical Analysis

Continuous variables and key time segments are expressed as median and interquartile range (IQR) due to skewed distribution of the data. Categorical variables are expressed as frequencies and percentages. The five categories of ambulatory status (full ambulation, minimal ambulation, ambulation with assistance, wheelchair bound and bedbound) were analyzed as frequencies and also collapsed into two categories defined as independent and dependent ambulation status. Independent ambulation status combined categories 4 and 5, and dependent ambulation status combined categories 1, 2 and 3. A change in ambulation status from baseline to discharge and from baseline to 30-day follow was calculated for each patient using the five-level variable. Improvement in ambulation status was defined as improvement of at least one category from the baseline finding excluding those who were fully ambulatory on admission and remained fully ambulatory at discharge and at 30-day follow-up (since they could not improve).

The “time from symptom onset to admission” and “time from admission to treatment” segments were categorized into 3 groups defined as <12 hours, 12-24 hours and >24 hours for ALI patients. Time to admission was categorized into 3 groups consisting of <1 month, 1-2 months and >2 months for CLI patients. A linear regression models were used to assess the associations between continuous (non-categorical) time segment variables and length of stay. A logistic regression models were used to assess the association between the categorized key time variables and short-term binary outcomes. Adjustment for age, sex, current smoking, hypertension, diabetes, hypercholesterolemia, history of CAD, CVD and PAD was performed in the linear and logistic regression models. Thirty-day amputation-free survival was investigated by Kaplan-Meier survival methods, with the Wilcoxon test used to compare groups. A Cox proportional hazards models were used to adjust for confounding factors in time-to-event data. A two-sided p-value of <0.05 was considered statistically significant. Statistical analysis was carried out using Stata/IC software version 10.1 (Stata, Inc. College Station, TX, USA).

5. RESULTS

5.1 Demographic Profile of Patients with Severe PAD

From February 2007 to December 2009, 206 patients with ALI (n=75) and CLI (n=131) were enrolled in the FRIENDS registry. Data lock for this analysis was February 2nd, 2010. At that time 202 (98%) completed the one month follow-up and 131 (64%) patients completed 6 months follow-up and 82 (40%) completed 12 months follow-up. Four patients were not reachable by multiple phone calls at one month follow-up, and medical record survey recorded no re-hospitalizations at the primary hospital or associated health system hospitals and the national death index website did not provide further information.

The total study cohort included 58.3% men and the median age was 76 years, with an interquartile range of 64 to 84 years for all patients. Detailed demographic characteristics and atherosclerosis risk factors of patients with severe PAD are shown in Table 1 and distinguished by their ALI or CLI clinical classification. A high proportion of patients were Caucasian and about 1 in 4 patients were obese. Current and former smoking was high and similar in both groups. A high proportion of patients had diabetes, hypertension, and hypercholesterolemia and the prevalence of these risk factors was similar in both groups. Atrial fibrillation (23.3%) was highly prevalent in these patients with severe PAD and was not different between the ALI and CLI cohorts. In this registry, no systematic effort was made to evaluate these patients for a hypercoagulable state or to assess the adequacy of anticoagulation in patients with known atrial fibrillation.

As expected, a history of CLI was more common in patients admitted for CLI as compared to ALI, and history of ALI was more common in patients admitted for ALI as compared to CLI. Overall, a history of established clinical PAD was high in patients admitted for ALI. Concomitant CAD was also highly prevalent in patients with severe PAD. The etiology of acute lower limb ischemia, as assessed by vascular specialty consultation and chart review, in this population is shown in Figure 1.

Thromboembolism, defined as inclusive of both embolism and acute *in situ* native artery occlusion, was deemed to account for the majority of acute limb ischemia. Fourteen out of 42 (33.3%) patients with ALI and a prior history of PAD presented with an acute native artery occlusion.

5.2 Initial Hospital Management

Initial hospital management included patients who did not undergo leg arterial revascularization ("medical management only"), those who underwent an endovascular or open surgical procedure, a combination of these two revascularization procedures, or primary amputation. The utilization rates for each of these treatment strategies are displayed in Table 2. Whereas the primary amputation rate was 9.7% low, the overall rate of in-hospital leg amputation was 21.4% and occurred more commonly in patients with CLI (25.9%) than ALI (13.3%). Of all amputations that were performed in ALI patients, major amputation was performed in 80% and was twice as common as in CLI patients (41.2%). In ALI patients, open surgical procedures were more commonly performed than endovascular procedures (44.0% vs. 34.7%). Similarly for CLI patients, open surgical procedures were more commonly performed than endovascular procedures (45.0% vs. 29.0%). A minority of patients (n=20, 9.7%) underwent percutaneous catheter-directed thrombolysis in combination with endovascular or surgical procedures. Catheter-directed thrombolysis was used more commonly in individuals with ALI (n=18, 8.7%) compared to individuals with CLI (n=2, 1.0%).

Atherosclerosis risk reduction medications were not used at target goals in this population. Use of atherosclerotic risk reduction medications did substantially increase from admission to discharge, but rates of use remained suboptimal at discharge, as shown in Table 3. In the ALI patients, antiplatelet use (single or in combination) was 62.7% on admission and increased to 82.2% at discharge. In the CLI patients, antiplatelet use was 73.3% on admission and increased to 86.9% at discharge. Warfarin use was 24.0% on admission and nearly doubled (45.2%) at discharge for ALI patients. In the CLI cohort, warfarin use was 26.7% on admission and increased to 32.6% at discharge. Statin use increased from 45.3% on admission to 61.6% at discharge for ALI patients. In CLI patients, statin use increased from 58.8% on admission to 69.8% at discharge. Of those individuals with documented atrial fibrillation, 56.3% of the patients were on warfarin on admission, including 35.3% of the ALI and 67.7% of the CLI patients. In the total sample, 48 (23.3%) patients were currently smoking on admission and of those 28 (58.3%) received documented smoking cessation counseling and or treatment at discharge. At the 30-day follow-up, 10 patients of those who received smoking cessation at discharge quit smoking resulting in a 32.2% self-reported success rate. Thirty-two (66.7%) patients continued to smoke and six patients stopped smoking by their own efforts or received counseling via their primary doctor.

5.3 Functional Status

At discharge, 40 (19.4%) patients were transferred to a rehabilitation institution, with these rates being similar in the ALI (n=14, 18.7%) and CLI (n=26, 19.9%) groups, respectively. Overall, 41 patients (19.9%) were discharged to a nursing home without rehabilitative facilities, with these rates being similar in the ALI (n=15, 20.0%) and CLI (n=26, 19.9%) groups. The detailed ambulation status data on admission, at discharge, and at 30 days is shown in Table 4. Full ambulation on admission substantially increased at discharge in patients with ALI (from 8.0% to 26.0%) and further increased at 30 days follow-up (to 47.0%). The fraction of patients who were bed bound on admission decreased substantially at discharge (from 41.3% to 12.3%) and continued to decrease at 30 days (to 3.0%). Minimal ambulation decreased at discharge and the fraction requiring ambulation with assistance and who were wheelchair bound increased at discharge. In the CLI patients, full ambulation on admission was 11.5% and decreased to 10.1% at discharge, but increased to 36.9% at 30 days follow-up. The fraction of CLI patients who were bed bound on admission decreased at discharge (from 4.6% to 3.9%) and continued to decrease at 30 days (to 0.8%). Minimal ambulation decreased at discharge, and the fraction who required ambulation with assistance and/or who required use of a wheelchair increased at discharge (Table 4).

A compiled clinically relevant functional status analysis was performed in which "independent ambulation" was defined when a patient enjoyed either full ambulation or minimal ambulation (in contrast to two additional “dependent ambulation” and “bedbound” status categories). In this analysis, “independent ambulatory” status increased from 49.3% on admission to 63.0% at discharge and to 78.8% at 30-day follow-up in surviving ALI patients (Table 5). Independent ambulation for surviving CLI patients however, decreased from 72.5% on admission to 52.7% at discharge, but then improved to 81.2% at 30 days follow-up.

Ambulatory status improved from baseline to discharge in 36 of 70 (51.4%) surviving patients with ALI defined by at least one ambulatory category improvement above the baseline status. Two deaths and three patients with full ambulation on admission who remained fully ambulatory at discharge were excluded from the analysis as there was no status change and inclusion would not be informative regarding clinical status improvement. At 30 days follow-up, ambulatory status improved in 43 of 64 (67.2%) surviving patients with ALI. Nine deaths and two patients with full ambulation on admission who remained fully ambulatory at 30 days were excluded from the analysis.

In CLI patients, ambulatory status improved in 12 of 124 (9.7%) surviving patients at discharge with at least one ambulatory category above the baseline status. Two deaths and five patients with full ambulation on admission who remained fully ambulatory at discharge were excluded from the analysis. At 30 days follow-up, ambulatory status improved in 44 of 111 (39.6%) surviving patients with CLI with at least one ambulatory category above the baseline status. Nine deaths and eleven patients with full ambulation on admission who remained fully ambulatory at 30 days were excluded from the analysis.

5.4 Key Time Segments and Short-term Outcomes

Time as a Predictive Factor for Short-term Outcomes in ALI

Time segments and ABI testing: Key time segments for patients with ALI are displayed in Table 6. Patients arrived at the hospital on average 19.2 hours after leg symptom onset and ranged between 1.3 hours and 10.1 days. The admission ankle-brachial index (ABI) measurement was performed within a median time of 3.8 hours;

heparin was administered within 2 hours; and a vascular specialist consultation was completed within 2.4 hours. However, only 23 (30.7%) ALI patients underwent an objective noninvasive evaluation of leg perfusion on admission (i.e., had an ABI or toe-brachial index, TBI; Table 7). As well, only 43 (57.3%) received in-hospital therapeutic heparinization prior to treatment. Thirteen patients received heparin prior to admission and of those patients who did not receive heparin (n=19), four were on warfarin prior to admission.

Hospital Length of Stay: The time from symptom onset to admission was evaluated in three categories, and patients in whom this category was below 12 hours, 12-24 hours, or more than 24 hours were observed to undergo in-hospital amputation in a stepwise increased manner, as is shown in Table 8. The time from symptom onset to admission was noted to be correlated with the hospital length of stay. In a linear regression model we found a stepwise increase in hospital length of stay. With every day increase in the duration of symptom, hospital stay was prolonged by 0.78 days ($p=0.01$). After multivariate adjustment for age, gender, CV risk factors, and clinical CAD, CVD, or PAD, there was still a significant linear association between time to admission and length of stay by 0.77 days per day increase in duration of ischemia ($p=0.013$). The time from admission to treatment also correlated with the length of hospitalization. With every day increase of time from admission to treatment, length of stay increased by 1.3 days ($p<0.001$). After multivariate adjustment, there was still a significant linear association between time of admission to treatment and length of hospital stay, so that for every day of delayed treatment the hospital stay increased by a 1.5 days ($p<0.001$).

Clinical endpoints: For ALI patients for whom the time of symptom onset to admission was below 12 hours, the quadruple endpoint at 30 days occurred in 3 out of 28 patients (10.7%). For patients in whom the time segment from "symptom onset to admission" was between 12-24 hours, this endpoint occurred in 1 out of 11 (9.1%). In patients in whom the "symptom onset to admission" segment was longer than 24 hours the quadruple endpoint occurred in 13 out of 36 patients (36.1%, as a statistically significant trend, $p=0.007$). Similar results were observed for amputation at 30 days ($P=0.011$), but no trend was observed for death at 30 days (Table 9). The time segment of “admission to revascularization” did not demonstrate a trend to predict all-cause death or the quadruple outcome endpoint (Table 9).

Time as a Predictive Factor for Short-term Outcome in CLI

For patients with CLI, median time segment for “symptom onset to admission” was 59.3 days with an interquartile range of 24.1 to 123.9 days (min. 6, max 2021 days). The median time from “symptom onset to treatment” was 60.9 with an interquartile range of 27.0 to 127.0 days. The median length of hospital stay was 6.1 with an interquartile range of 3.1 to 10.7 days. There was no association of the key time segments to in-hospital amputation or length of stay for CLI patients (Table 10). No association was observed between the key time segments of “symptom onset to admission” and amputation, all-cause death or the quadruple endpoint at 30-day follow-up (Table 11). Although the difference was not significant, CLI patients who presented with rest pain at hospitalization were more likely to have a shorter “symptom onset to admission” time and lesser in-hospital amputation rate, and shorter hospital length of stay than those patients who presented with an ischemic ulcer or gangrene (Table 12). The 30-day amputation free survival was significantly better for patients who presented with ischemic rest pain (82.9%) than those with a foot ulcer or gangrene (66.7%, Wilcoxon P=0.039, Fig. 2). Adjustment for multivariate factors in a Cox proportional hazards model confirmed the significant difference (P=0.037).

Amputation rates and hospital length of stay were similar for both genders in the ALI and CLI cohorts.

5.5 Systemic Outcomes at 30 Days Follow-Up

Rates of non-fatal MI and stroke, amputation and death at 1, 6 and 12 months of follow-up are shown in Table 13, thought the incomplete follow-up for these outcome measures at 6 and 12 months is noted. Overall, amputation-free survival at 30 days was 78.7% for patients with ALI and 71.8% for patients with CLI (Fig. 3).

Systemic Outcome for ALI

For patients with ALI, there were no MI or stroke events observed at one month. The 30 day amputation rate was 14.7% overall, of which 13.3% of the total were for major amputation. The thirty day all-cause death rate was 12%. Rehospitalization for CV and non-CV events was 9.3% and 8%, respectively. ALI or CLI recurrence was 5.6%; the combined triple outcome event rate for nonfatal MI, stroke or amputation was 14.7%; and the combined quadruple outcome endpoint rate for nonfatal MI, stroke amputation or death was 22.7%.

Systemic Outcome for CLI

For CLI patients, the 30 day non-fatal MI event rate was 0.8%, no stroke occurred, but minor and major amputation occurred in 29% and major amputation occurred in 11.5% of this population. 30 days death occurred in 6.9% and was less frequent than patients with ALI. Rehospitalization for CV and non-CV events was 6.1% and 16.8%, respectively. ALI or CLI recurrence was 7.6% and the combined triple outcome event rates for nonfatal MI, stroke or amputation was 29%. The combined quadruple outcome measure for nonfatal MI, stroke amputation or death was 33.6%.

6. DISCUSSION

6.1 Time as a Predictive Factor for Adverse Systemic Outcomes

This prospective PAD registry assessed the association between the onset of clinical symptoms of ALI/CLI and time to treatment on both cardiovascular and limb ischemic outcomes (including amputation) and explores whether these key time segments served as a previously undefined predictor of both limb and patient survival. Our results suggest that increased duration of ischemia was significantly associated with in-hospital amputation and length of hospital stay among patients with ALI. Among CLI patients no association was found between symptom onset and either in-hospital amputation rates or length of stay.

Our findings among patients with ALI were consistent with other studies reporting duration of ischemia as a crucial risk factor determining limb survival.[17-18] Another study suggested that ALI-related mortality was increased with delay in treatment of ischemia, significant underlying atherosclerosis, and poor arterial back bleeding at operation.[38] The high mortality rate was also associated with age as highlighted in a study of 84 ALI patients older than 75 years old. The authors found that overall 30-day mortality rate was 42%.[39] Our 30-day mortality rate was 12% which is low and might be explained by the expedited revascularization strategy and reasonable use of risk reduction medications.

Interestingly, this cohort of patients with ALI comprised an elderly population with a median age of 73 years. It is notable that approximately 1 in 4 patients presented with atrial fibrillation. Similar results have been reported in an administrative data set of the University of Michigan Hospital where the investigator found a 25% rate of "dysrhythmia" in patients with ALI.[40] It would be interesting to determine whether atrial fibrillation in this cohort was established or newly diagnosed in this high risk population. However, our database did not include this piece of information. Moreover, more than 50% do have a history of PAD or CAD and 1 in 5 do have CVD, thus suggesting the poly-morbidity of these patients with high atherosclerotic burden. It is often assumed that ALI occurs in younger individuals without known atherosclerosis, but our results suggest the contrary. This might, in part, explain the high fatality rate of ALI as highlighted in the study of Aune et al where 5-year mortality rate ranged between 56 to 83% pending on the cause of ALI.[2] Rates of native artery occlusion in patients with prior PAD were also quite high in this study, ranging at the upper limit compared to the experience of others who have reported a range from 7% to 30% of ALI in chronic PAD.[9]

Average hospital length of stay estimated for ALI patients has been reported to be approximately 10 days.[40-42] We found an average length of hospitalization of around a week, which is substantially lower than what has been published, thus supporting our hypothesis that early admission and treatment of ALI might be beneficial reducing the length of hospital stay.

Surgical catheter-directed thrombolysis, thromboembolectomy and bypass grafting are the mainstays of therapy. Three landmark randomized, prospective clinical trials of patients with ALI published in the 1990's suggested that thrombolytic therapy was equivalent to surgical therapy regarding limb salvage.[43-45] Because the major thrombolytic trials failed to demonstrate an improved outcome for catheter-directed thrombolysis compared to open surgery, clinical consensus was never achieved. Physicians continue to offer patients therapy based on their field of expertise and patient symptoms.

Thus, regardless of revascularization modality used, the essential aspects of timely reperfusion for the ischemic leg remain controversial and worthy of study. This would be best achieved by creation of a structured care pathway to decrease mortality and amputation, in a manner analogous as shown to programs now modeled to provide care for individuals with an MI to decrease mortality by shortening "door to balloon" times as a standard of care.[46] Similarly, the early reperfusion of acute ischemic stroke within 3 hours has been established[47] and recent studies recommend urgent assessment and treatment of patients with transient ischemic attack as well as minor stroke to reduce subsequent hospital bed-days, acute costs, and 6-month disability.[48-49] Evidence is mounting that the time factor in ALI might also contribute to both limb and patient survival. Selected biological reasons for this include prolonged leg muscle ischemia that causes metabolic changes with increased creatine phosphokinase, which is known to confer an increased risk of major amputation.[50] Thus, a similar policy that would create and disseminate a structured ALI/CLI health care pathway should be adopted for widespread use for managing patients with ALI. However, large-scale trials are needed to further elucidate the early time frame benefit. Although this Registry did not document any association of symptom and treatment time segments, for patients with CLI, and in-hospital amputation or length of stay, we recognize that the time from symptom onset to admission is far too long and efforts should be directed in shortening this time frame. This lack of association might be explained by the heterogeneity of the CLI population or small sample size.

In our study, 43 (57.3%) of patients with ALI had therapeutic heparin prior to treatment and 13 (17.3%) patients of the total received therapeutic heparin outside the hospital. Once the diagnosis of ALI is established, institution of adequate systemic anticoagulation with unfractionated heparin is standard treatment as this has been shown to reduce morbidity and mortality compared with not using anticoagulation.[5-6, 51] The goal of anticoagulation is to decrease the risk of thrombus propagation and in case of presumed embolic occlusion, to prevent recurrent embolization. Overall, 19 (25.3%) patients did not receive therapeutic heparinization prior to revascularization. This might be explained by the fact that four of these patients were on warfarin and early revascularization was instituted, thus withholding anticoagulation. In CLI patients, no data are available that had evaluated the net benefit or harm of use of unfractionated heparin prior to revascularization and thus this issue remains to be addressed in future studies. An expedited revascularization is generally recommended in these patients to preserve limb salvage. The bypass versus angioplasty in severe ischemia of the leg (BASIL) trial addressed the question whether an endovascular first or a surgery first strategy would be more beneficial in terms of amputation-free survival. The authors randomized 452 patients with CLI to either treatment and found that amputation-free survival at 2 years was not significantly different in both strategies, thus suggesting that no matter what revascularization modality is used, the importance is that revascularization is attempted.[52]

6.2 Risk Factor Reduction

Comorbidities are highly prevalent in patients with severe PAD, thus suggesting a more generalized atherosclerotic burden affecting several vascular territories that potentially leads to the high ischemic vascular events. Atherosclerotic risk factors are highly prevalent in patients with ALI and CLI, as observed in our study. However, risk factor reduction therapies are used only incompletely prior to admission, as at discharge only 60% of these patients with severe PAD received antiplatelet and 61% statin therapies at discharge for ALI patients. CLI patients were comparably undertreated as only 57% were prescribed antiplatelet and 69% statin therapy at discharge. This might confer increased high risk of CVD morbidity and mortality, especially in patients with CLI in whom the primary amputation rate varies between 10 and 40% within a year after diagnosis,[19] and the one and five-year mortality rates are between 20-25% and 40-70%, respectively.[29-30] These data are concordant with the documentation of underutilization of evidence-based medications as was shown first in the PAD population enrolled in the PARTNERS study.[34] In PARTNERS,[34] PAD patients were less likely to be prescribed antihypertensive (77% vs. 95%), lipid-lowering (56% vs. 73%) and antiplatelet (54% vs. 71%) therapies as compared to CAD patients. PAD patients enrolled in the international REACH registry[53] were also less likely to be treated with antihypertensive, lipid-lowering and antiplatelet therapies than CAD patients. The underuse of evidence-based PAD treatment is a worldwide problem and has been well documented in the U.S.,[54] United Kingdom,[55] France[56] and China.[57] One might think that the most severe PAD population who are at high risk of subsequent vascular ischemic events would receive more attention in evidence-based risk reduction medical treatment but studies report that even patients with CLI were found to be undertreated with antihypertensive, lipid-lowering and antiplatelet medications[58-59] and our study is no exception. Underuse of statin in CLI patients was reported in 46% in the Coronary Artery Revascularization Prophylaxis (CARP)[60] and in the Project of Ex-Vivo vein graft Engineering via Transfection III (PREVENT III)[58] trial. Similar results (36%) were found in the BASIL trial.[52] Although statin use in our CLI population increased from 59% on admission to 67% at discharge, treatment was incomplete and remains an area for future improvement.

An interesting finding of our study was that of the 48 patients (23.3%) who were current smokers on admission, 28 (58.3%) received smoking cessation counseling and or treatment at discharge. At 30-day follow-up, 66.7% of these patients continued to smoke, suggesting that either smoking cessation counseling and or treatment were not effective. It might be assumed that the limb- and life-threatening leg ischemic event was not recognized as truly life threatening. It remains unclear whether the contribution of tobacco use to both PAD and CLI incidence is well known. If this link is not appreciated by the patient, referral times and post-discharge outcomes might be anticipated to be worse. In fact, studies have shown that less than half of patients understand the relation between PAD and smoking.[61] Smoking cessation counseling and treatment is a cornerstone in the management of patients with PAD and should be instituted regularly, as studies have demonstrated a higher achievement of abstinence in patient populations encouraged by their physicians to quit, as compared to those who received no counseling from a health care provider.[62]

Another interesting finding was that among the severe PAD patients who were hospitalized, 36.4% were patients with acute limb ischemia resulting in an ALI/CLI ratio of approximately 1:2. Every third patient with severe PAD presented with acute limb ischemia with impending limb loss. No contemporary data (registry or clinical trial) has reported the relative fraction of ALI and CLI in a clinical cohort. Table 14 provides a summary of the ALI/CLI ratio at a population level and at the single center level; it is notable that prior estimates correlate well with our data. Thus, while many vascular specialists believe that ALI is rare, our data demonstrate that it is nearly as common as CLI.

6.3 Functional Status

There is no single recognized system used consistently to report functional status in individuals with lower extremity disease, limiting the comparison of these data to prior studies. Functional status improved by at least one category above baseline in 49.3% of patients at discharge and in 65.2% of patients at 30 days follow-up in ALI patients. CLI patients improved at discharge at a much lower rate (9.3%), but substantial improvement was observed in 31.1% of subjects at 30 days follow-up. Other investigations have reported a 99% rate of independent living in patients post-discharge amongst those individuals lived independently preoperatively and 97% of the patients who were ambulatory preoperatively remained ambulatory after hospital discharge.[63] Taylor et al[64] evaluated retrospective functional outcomes at 5 years in 1000 patients undergoing revascularization for CLI and found that 70.6% maintained an independent ambulatory status. The investigator defined functional status as “ambulatory” (independent ambulation out of house), “ambulatory/homebound” (ambulatory in the home only) and “nonambulatory/transfer”. Similarly, Nehler et al[32] defined ambulatory status categorically as “outdoors”, “indoors”, or “nonambulatory”. He reported a series of major lower extremity amputations at 10 months in 21% of patients who ambulated outdoors, as compared to rates of 28% for the “indoors only” and 51% amputation rate in individuals who were “nonambulatory”. Chung et al[65] defined ambulatory status similarly to Nehler and reported on outcomes for 334 patients undergoing infrainguinal bypass for CLI. In his series, outdoor ambulation decreased to 72% at 6 months compared to 91% at baseline. In addition Nehler and Chung defined baseline functional status as the level of function within 30 days before the onset of CLI and Taylor defined functional status immediately before the onset of symptomatic leg arterial disease. In contrast, we defined baseline functional status after onset of severe PAD and within one week before admission. In addition, we felt that categorizing functional status in 3 categories would not reflect all possible functional outcomes of these patients. Thus, we initially used 5 functional categories to assess the functional outcome and have thus far only evaluated changes that were achieved between baseline to discharge and 30 days follow-up.

In this context, the lack of consensus on how to best assess and report the functional status in patients with ALI/CLI makes inter-population comparison challenging. In this population, no disease-specific questionnaires have been validated in reporting functional outcomes in severe PAD patients. The Nottingham Health Profile questionnaire provides an assessment of pain, physical mobility, sleep, emotional reactions, energy, and social isolation and has been most widely used in patients with less severe PAD[66]. This tool has been reported to be more responsive to change in patients with CLI.[67] However, this questionnaire was not considered appropriate for use to assess the ambulatory status of this cohort during a telephone survey in a short and informative manner.

6.4 Limitations of this Study

There are limiting factors (e.g., selection bias) that are inherent in most observational clinical studies and our study is no exception. This study was conducted at a tertiary vascular referral center and thus definitely is associated with a “health system-based” selection bias. As well, the majority of patients in this registry were Caucasian, reflecting the Minnesota population and thus the generalizability of these data are limited to any non-white population (in whom ALI and CLI are known to be more common). Furthermore, in this registry endovascular and open surgical revascularization procedures were performed at about the same rate. This rate and associated outcomes thus may not be comparable to other centers that provide more aggressive use of endovascular revascularization approaches. Nevertheless, we know of no data that would confirm that the choice of revascularization approach would differentially affect limb outcomes, and systemic rates of periprocedural MI, stroke and death were very low in this series. Clearly, the choice of revascularization approach might affect hospital length of stay.

The categorization of the time segments into three groups was based, in part, on the distribution of our time data, and in part of the precedent set in the scant published literature. While this categorization scheme makes intuitive sense, it is biologically arbitrary.

We have noted the shortcoming in current subjective methods of assessing functional status in this population, which was based on the ability of patients to independently perform activities of daily living. As such, there is considerable variability at baseline in this elderly population with many co-morbid conditions. Such variability and lack of a validated tool for patients with CLI (in contrast to use of an objective, validated scoring system) to assess functional status makes accurate interpretation of short-term change difficult. We note that "ambulatory status" is a mere sub-category of global function, which would be preferable for use in future CLI research studies.

This registry included a relatively limited sample of patients; thus, a series of type II errors might occur, which would be less likely in a larger study. Nevertheless, we note that this series comprises one of the larger such observations presented in the literature and this sample provides a template for future study expansion.

The strengths of our study lie in the first description of a "guideline-driven" ALI/CLI health care pathway and implementation of a multidisciplinary approach in a tertiary vascular care center to evaluate the theoretical clinical time frame benefit. As well, despite these limitations, such a registry offers insight into the real-world management of patients with ALI and CLI and highlight gaps for future study. These data demonstrate that ALI is not rare among patients with severe PAD. Thus, these pilot data provide health care systems with an opportunity to create a systematic standard of care to improve limb and patient survival, and perhaps shorten hospitalization time and thus lower health economic costs.

7. CONCLUSIONS

7.1 Pre-Hospital

- The ALI/CLI case mix syndrome distribution is not what would be anticipated. ALI, as defined using bedside clinical definitions, is surprisingly common. Future research should verify or refute this ALI frequency by confirming the accuracy of the diagnosis by objective vascular testing, or to clarify the mis-classification rate.
- The prevalence of embolic arterial disease is very high, use of prophylactic anticoagulation is incomplete, and the relation of untreated or new AF to limb threat is evident. Future research might focus on the potential utility of proactive detection and treatment of AF in individuals with PAD so as to lower rates of ALI/CLI presentation.
- Pre-hospital referral times for individuals with severe PAD are very long, especially for patients with CLI. Future research with an expanded population derived from a multi-center registry could clarify if this length of time does or does not relate to any severe adverse outcomes.

7.2 In-Hospital

- On admission, established PAD and other atherosclerotic diseases are common (these are not *"de novo"* cases; in contrast, these patients are "in the health system"), but use of proven risk reduction treatments was poor.

- Despite creation of a pilot ALI/CLI health care pathway, the within-hospital initiation of risk reduction medical interventions is low and remained incomplete at discharge. Future study might evaluate methods to improve use of these medical interventions (e.g., triggered electronic medical record reminders, or "pay for performance", or NP-driven pre-discharge rounds) so as to lower rates of cardiovascular and limb ischemic events.
- Diagnostic use of objective limb perfusion measures (e.g., the ABI or TBI) was low, and was measured in 32.5% of patients on admission and 29.6% of patients at discharge. Thus, misclassification of patients with rest pain as "ischemic" or non-ischemic seems likely. Measurement of rates of misclassification may merit further study.
- Early admission and treatment of patients with severe PAD appears to be significantly associated with lower in-hospital amputation rates and a shorter length of stay. These data, if confirmed, would have potentially major implications for health outcomes and health care costs in this population.
- The measured time segment from "admission to revascularization" is reasonable for individuals with ALI, but nevertheless could be shortened. Efforts to achieve more efficient hospitalization usage might now be devised using extant hospital system methods.
- Rates of primary amputation were low. Nevertheless, a high one week 25% amputation rate implies that revascularization is not uniformly associated with full "limb salvage". The impact of revascularization on limiting the level or extent of amputation cannot be determined from this dataset. If this registry were expanded, heterogeneities in hospital-based revascularization rates and differential use of revascularization methods might elucidate major impacts on limb, systemic, and functional outcomes.

7.3 Post-Hospital

- Early admission and treatment of individuals with severe PAD is associated with a reduced short-term amputation rate and lowered rate for the quadruple endpoint of nonfatal MI, stroke, amputation, and death at 30 days for ALI patients.
- Early admission did not reduce the 30-day amputation or quadruple endpoint rate for individuals with CLI.
- The clinical presentation of "ischemic rest pain" in CLI patients is associated with a better amputation-free survival than for individuals who present with an ischemic ulcer or gangrene. This may represent either an earlier stage of a comparably severe limb perfusion deficit (foot "unstable angina" vs. "infarction") or represent misclassification of the cause of pain in a fraction of this cohort.
- Independent functional status improved from 49% on admission to 79% at 30 days follow-up for individuals with ALI. Independent functional status improved from 73% on admission to 81% at 30 days follow-up for individuals with CLI.
- These data demonstrate low short-term rates of non-fatal MI, stroke, or death at 30 days of 0%, 0%, 12% for ALI and 1%, 0%, 6.9% for CLI, respectively, in this severe PAD population.
- These data demonstrate high short-term rates of nonfatal MI, stroke or amputation of 14.7% and 29% for individuals with ALI and CLI, respectively.
- These data demonstrate high short-term rates of the quadruple endpoint (nonfatal MI, stroke, amputation or death) was 22.7% and 33.6% for individuals with ALI and CLI, respectively.
- The one month rate of major amputation is high at 13.3% and 11.5% for patients with ALI and CLI, respectively.
- The one month recurrence rate of a new ALI or CLI episode in patients discharged with severe PAD was 5.6% and 7.6% for ALI and CLI, respectively.
- The one month health utilization (readmission for a cardiovascular ischemic event) was 9.3% and 6.1% for ALI and CLI, respectively.

7.4 Health Implications and Future Investigational Directions

- Little evidence exists that demonstrates the potential health and health economic benefit of treating ALI in a timely manner. These results suggest that expedited admission and treatment are associated with a reduced amputation rate, shorter hospital length of stay, and lower 30 day cardiovascular morbidity and mortality. Such observational data require confirmation from an interventional clinical trial. Future research might be directed towards implementing an algorithm for delivering systematic care (expedited vs. "usual care") to verify this potential benefit. If confirmed, this would demonstrate the parallel health care improvements that could accrue to individuals with PAD, as compared to patients who suffer an MI or stroke.
- Use of risk reduction therapies is low in a vascular health care delivery system that emphasizes revascularization, but that does not provide incentives to medical caregivers to deliver proven cardiovascular therapies. Assessment of the efficacy of educational and process of care interventions to improve the rate of use of established cardioprotective medications is warranted.
- Similarly, tobacco cessation strategies can be effective during a severe PAD hospitalization, although the longer-term (6 month) efficacy of these interventions (the "severe PAD teachable moment") and verification of self-reported quit rates is required.
- Continuous outreach and education of both current PAD patients and their health care providers would likely be required to assure that episodes of ALI and CLI are promptly recognized; that short-term rates of CVD events are known; and so that recurrence rates might be minimized.
- Expansion of the ALI/CLI registry to a multicenter program would provide a higher sample size and unique opportunity to assess these trends and then provide an organizational substrate to test specific process of care interventions. A larger (multi-thousand) ALI-CLI patient registry would confirm the adverse natural history provided by the current dataset, and permit subgroup analysis of additional populations at risk (Hispanic, Black, and Native American, and other subgroups).

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LIST OF TABLES

Table 1. Baseline characteristics and atherosclerosis risk factors of patients with severe PAD

Characteristic	**Number (%)***		
	Total (n=206)	**ALI (n=75)**	**CLI (n=131)**
Men	120 (58.3)	38 (50.7)	82 (62.6)
Age, median (IQR), years	76 (64, 84)	73 (61, 84)	76 (65, 84)
Ethnicity			
Caucasian	194 (94.2)	73 (97.3)	121 (92.4)
African-American	8 (3.9)	1 (1.3)	7 (5.3)
Other	4 (1.9)	1 (1.3)	3 (2.3)
Atherosclerosis risk factors			
Overweight (BMI 25-30 kg/m^2)	66 (32.0)	28 (37.3)	38 (29.0)
Obesity (BMI ≥30 kg/m^2)	55 (26.7)	20 (26.7)	35 (26.7)
Current smoker	48 (23.3)	15 (20.0)	33 (25.2)
Former smoker	92 (44.7)	29 (38.7)	63 (48.1)
Diabetes	91 (44.2)	29 (38.7)	62 (47.3)
Hypertension	167 (81.1)	55 (73.3)	112 (85.5)
Hypercholesterolemia	132 (64.1)	46 (61.3)	86 (65.7)
Atrial fibrillation	48 (23.3)	17 (22.7)	31 (23.7)
Comorbidities			
History of PAD	148 (71.8)	42 (56.0)	106 (80.9)
History of CLI	45 (21.9)	8 (10.7)	37 (29.5)

History of ALI	10 (4.9)	7 (9.3)	3 (2.3)
History of CAD	114 (55.3)	38 (50.7)	76 (58.0)
History of MI	55 (26.7)	22 (29.3)	33 (25.2)
History of CABG	36 (17.5)	11 (14.7)	25 (19.1)
History of CVD	41 (19.9)	16 (21.3)	25 (19.1)
History of Stroke	24 (11.7)	6 (8.0)	18 (13.7)
History of TIA	15 (7.3)	9 (12.0)	6 (4.6)
Carotid artery stenting/endarterectomy	10 (4.9)	3 (4.0)	7 (5.3)

*If not otherwise specified.
ALI, acute limb ischemia; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CLI, critical limb ischemia; CVD, cerebrovascular disease; MI, myocardial infarction; PAD, peripheral artery disease; TIA, transient ischemic attack.

Table 2. In-hospital management of patients with severe PAD

	Number (%)		
	Total (n=206)	**ALI (n=75)**	**CLI (n=131)**
Revascularization			
No revascularization	19 (9.2)	6 (8.0)	13 (9.9)
Endovascular procedure	64 (31.1)	26 (34.7)	38 (29.0)
Open surgical procedure	92 (44.7)	33 (44.0)	59 (45.0)
Primary amputation	20 (9.7)	5 (6.7)	15 (11.5)
Surgical and endovascular procedure	11 (5.3)	5 (6.7)	6 (4.6)
Amputation			
All amputation	44 (21.4)	10 (13.3)	34 (25.9)
- Minor	22 (10.7)	2 (2.7)	20 (15.3)
- Major	22 (10.7)	8 (10.7)	14 (10.7)
- Major below-knee	13 (6.3)	3 (4.0)	10 (7.6)
- Major above-knee	9 (4.4)	5 (6.7)	4 (3.1)

Table 3. Use of risk reduction medical treatments stratified by ALI and CLI subgroups

	Number (%)			
	ALI		CLI	
Medication	Admission N=75	Discharge N=73	Admission N=131	Discharge N=129
ASA or clopidogrel	35 (46.7)	45 (61.6)	79 (60.3)	74 (57.4)
ASA and clopidogrel	12 (16.0)	15 (20.6)	17 (13.0)	38 (29.5)
Warfarin	18 (24.0)	33 (45.2)	35 (26.7)	42 (32.6)
Statin	34 (45.3)	45 (61.6)	77 (58.8)	90 (69.8)
Other lipid lowering agents	7 (9.3)	4 (5.5)	10 (7.6)	9 (7.0)
ACE/ARB	34 (45.3)	35 (48.0)	75 (57.3)	75 (58.1)
Beta blocker	42 (56.0)	51 (69.9)	88 (67.2)	101 (78.3)

ACE/ARB; angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; ASA, acetylsalicylic acid

Table 4. Functional status on admission, discharge and at 30 days in surviving patients stratified by ALI and CLI

	Number (%)					
	ALI			CLI		
Functional status	**Admission N=75**	**Discharge N=73**	**30 days N=66**	**Admission N=131**	**Discharge N=129**	**30 days N=122**
Unlimited ambulation	6 (8.0)	19 (26.0)	31 (47.0)	15 (11.5)	13 (10.1)	45 (36.9)
Minimally ambulatory	31 (41.3)	27 (37.0)	21 (31.8)	80 (61.1)	55 (42.6)	54 (44.3)
Ambulation with assistance	2 (2.7)	8 (11.0)	2 (3.0)	9 (6.9)	18 (14.0)	2 (1.6)
Wheelchair bound	5 (6.7)	10 (13.7)	10 (15.2)	21 (16.0)	38 (29.5)	20 (16.4)
Bed bound	31 (41.3)	9 (12.3)	2 (3.0)	6 (4.6)	5 (3.9)	1 (0.8)

Table 5. Independent and dependent ambulatory status on admission, discharge and 30 days in surviving patients stratified by ALI and CLI

	Number (%)					
	ALI			CLI		
Functional status	**Admission N=75**	**Discharge N=73**	**30 days N=66**	**Admission N=131**	**Discharge N=129**	**30 days N=122**
Independent ambulation	37 (49.3)	46 (63.0)	52 (78.8)	95 (72.5)	68 (52.7)	99 (81.2)
Dependent ambulation	38 (50.7)	27 (37.0)	14 (21.2)	36 (27.5)	61 (47.3)	23 (18.8)

Table 6. Key time segments for patients with ALI

Key time segments	ALI (n=75) Median (25th, 75th)
Symptom onset to admission	19.2 (7.2, 79.2)
Admission to ABI*	3.8 (2.5, 7.1)
Admission to heparin**	2.0 (1.1, 4.8)
Admission to vascular specialist at bedside	2.4 (1.1, 6.0)
Admission to revascularization	14.0 (4.4, 27.7)
Length of stay (days)	7.0 (4.3, 10.4)

Note: Key time segments are given in hours if not otherwise stated. ABI, ankle-brachial index
*23 (30.7%) patients had ABI performed on admission.
** 43 (57.3%) patients had therapeutic heparin prior to revascularization.

Table 7. Frequency of use of ankle-brachial index measurements among severe PAD patients

	Number (%)		
	Total	ALI	CLI
Admission, n=206	67 (32.5)	23 (30.7)	44 (33.6)
Discharge, n=202	61 (30.2)	22 (30.1)	39 (30.2)
Meet European consensus definition*	27 (13.1)	6 (8.0)	21 (16.0)
ABI ≤0.4	48 (23.3)	17 (22.7)	31 (23.7)

*European consensus definition: ankle pressure ≤50 mmHg or toe pressure ≤30 mmHg
ABI, ankle-brachial index

Table 8. Association of key time segments and in-hospital amputation among patients with ALI

	Symptom onset to admission (n=75)			
	<12-hour	12-24-hour	>24 hour	P for trend
Amputation, n/N (%)	0/28 (0)	1/11 (9.1)	9/36 (25)	0.015
Length of stay, median days and IQR	6.9 (3.1, 10.7)	6.0 (4.7, 7.0)	8.4 (5.4, 12.1)	0.024
	Admission to revascularization (n=69)*			
	<12-hour	12-24-hour	>24 hour	
Length of stay, median days and IQR	7.0 (4.3, 10.4)	6.5 (4.3, 8.4)	7.3 (5.1, 13.6)	0.15

*Note: 6 (8%) did not undergo revascularization.
P for trend adjusted for age, gender, CV risk factors, CAD, CVD, PAD.
IQR denotes interquartile range.

Table 9. Association of key time segments and 30-day outcomes stratified by <12hrs, 12-24hrs and >24hrs duration of ischemia in ALI

	Symptom onset to admission (n=75)			
	<12-hour	12-24-hour	>24 hour	P for trend
Amputation at 30 days, n/N (%)	0/28 (0)	1/11 (9.1)	10/36 (27.8)	0.011
Death at 30 days, n/N (%)	3/28 (10.7)	1/11 (9.1)	5/36 (13.9)	0.18
Nonfatal MI, stroke, amputation or death at 30 days, n/N (%)	3/28 (10.7)	1/11 (9.1)	13/36 (36.1)	0.007
	Admission to revascularization (n=69)*			
	<12-hour	12-24-hour	>24 hour	
Death at 30 days, n/N (%)	2/33 (6.1)	2/12 (16.7)	3/24 (12.5)	0.79
Nonfatal MI, stroke, amputation or death at 30 days, n/N (%)	5/33 (15.2)	2/12 (16.7)	7/24 (29.2)	0.24

*Note: 6 (8%) did not undergo revascularization.
P-value adjusted for age, gender, CV risk factors, CAD, CVD, PAD.

Table 10. Association of key time segments and in-hospital amputation among patients with CLI

	Symptom onset to admission (n=131)			
	<1 mo	1-2 mo	>2 mo	P for trend
Amputation, n/N (%)	11/44 (25)	7/27 (24.1)	16/58 (27.6)	0.58
Length of stay, median days and IQR	6.5 (4.0, 9.1)	7.3 (3.2, 14.0)	5.6 (2.9, 10.7)	0.07
	Symptom onset to revascularization (n=118)*			
	<1 mo	1-2 mo	>2 mo	
Length of stay, median days and IQR	7.0 (4.2, 9.0)	6.1 (2.9, 10.3)	6.1 (2.9, 11.1)	0.24

*Note: 13 (9.9%) did not undergo revascularization or primary amputation.
P for trend adjusted for age, gender, CV risk factors, CAD, CVD, PAD.

Table 11. Association of key time segments and 30-day outcomes stratified by <1 mo, 1-2 mo, >2 mo duration of ischemia in CLI

	Symptom onset to admission (n=131)			
	<1 mo	1-2 mo	>2 mo	P for trend
Amputation at 30 days, n/N (%)	14/44 (31.8)	7/29 (24.1)	17/58 (29.3)	0.96
Death at 30 days, n/N (%)	2/44 (4.5)	3/29 (10.3)	4/58 (6.9)	0.56
Nonfatal MI, stroke, amputation or death at 30 days, n/N (%)	14/44 (31.8)	10/29 (34.5)	20/58 (34.5)	0.55
	Symptom onset to revascularization (n=118)*			
Amputation at 30 days, n/N (%)	9/31 (29.0)	10/30 (33.3)	19/57 (33.3)	0.5
Death at 30 days, n/N (%)	2/31 (6.5)	2/30 (6.7)	1/57 (1.8)	0.27
Nonfatal MI, stroke, amputation or death at 30 days, n/N (%)	9/31 (29.0)	12/30 (40.0)	19/57 (33.3)	0.72

*Note: 13 (9.9%) did not undergo revascularization or primary amputation.
P-value adjusted for age, gender, CV risk factors, CAD, CVD, PAD.

Table 12. Clinical presentation and association with short-term outcomes in patients with CLI

	Symptom onset to admission (days)	In-hospital amputation (%)	Length of stay, days (IQR)
Rest pain (n=41)	31 (21, 95)	14.6	5.1 (3.0, 8.9)
Ulcer or gangrene (n=90)	61 (30, 127)	42.2	6.2 (3.3, 11.1)
P-value	0.1	0.085	0.1

Note: Time given in median days and interquartile range.
P-value adjusted for age, gender, CV risk factors, CAD, CVD, PAD.

Table 13. Short- and long-term outcomes stratified by ALI and CLI

	Number (%)					
	Acute Limb Ischemia			Critical Limb Ischemia		
	1 mo	6 mo	12 mo	1 mo	6 mo	12 mo
Follow-up at time of data lock	96%	56%	41%	99%	68%	40%
MI	0	0	0	1 (0.8)	3 (2.3)	3 (2.3)
Stroke	0	2 (2.7)	5 (6.7)	0	3 (2.3)	4 (3.1)
All amputation	11 (14.7)	12 (16.0)	13 (17.3)	38 (29.0)	43 (32.8)	45 (34.4)
Major amputation	10 (13.3)	10 (13.3)	11 (14.7)	15 (11.5)	17 (13.0)	20 (15.3)
Death	9 (12.0)	12 (16.0)	15 (20.0)	9 (6.9)	16 (12.2)	19 (14.5)
Rehosp for CV events*	7 (9.3)	11 (14.7)	14 (18.6)	8 (6.1)	23 (17.6)	23 (17.6)
Rehosp non-CV events	6 (8.0)	17 (22.7)	22 (29.3)	22 (16.8)	36 (27.5)	43 (32.8)
ALI/CLI recurrence	5 (5.6)	7 (9.3)	9 (12.0)	10 (7.6)	25 (19.1)	32 (24.4)
Nonfatal MI, stroke, amputation	11 (14.7)	14 (18.7)	18 (24.0)	38 (29.0)	46 (35.1)	48 (36.6)
Nonfatal MI, stroke, amputation, death	17 (22.7)	21 (28.0)	25 (33.3)	44 (33.6)	57 (43.5)	59 (45.0)

ALI, acute limb ischemia; CLI, critical limb ischemia; CV, cardiovascular; MI, myocardial infarction; mo, month; rehosp, rehospitalization; *CV events defined as TIA, unstable angina, worsening of PAD but not ALI or CLI, CHF, other ischemic arterial event or bleeding leading to both hospitalization and transfusion

Table 14. The literature-based fraction of ALI among severe PAD

Author	Country	Year	Disease	Definition	Cases	ALI/CLI ratio
Population study						
Davies[7]	UK	1997	ALI	Sudden deterioration in the circulation of a previously symptom-free limb	166/million/y	
Rothwell[21]	UK	2005	CLI	Rest pain, ulcer or both	340/million/y	
VSSGB* and Ireland[20]	UK	1995	CLI	Degree of ischemia which, in the opinion of the surgeon, would have been likely to necessitate amputation of the limb in the absence of successful revascularization.	400/million/y	33% / 29%
Single center study						
Hartung[68]	France	2005	ALI	ALI category I- IIa	4	22%
			CLI	Rutherford 4, 5	14	
Alimi[69]	France	2008	ALI	ALI category I-IIb	20	38%
			CLI	Rutherford 4, 5	32	
FRIENDS** registry	USA	2010	ALI	Sudden decrease in limb perfusion causing threat to limb viability within 14 days	75	36%
			CLI	Rutherford 4, 5, 6	131	

*Vascular Surgical Society of Great Britain and Ireland. **FReedom from Ischemic Events: New Dimension for Survival.

LIST OF FIGURES

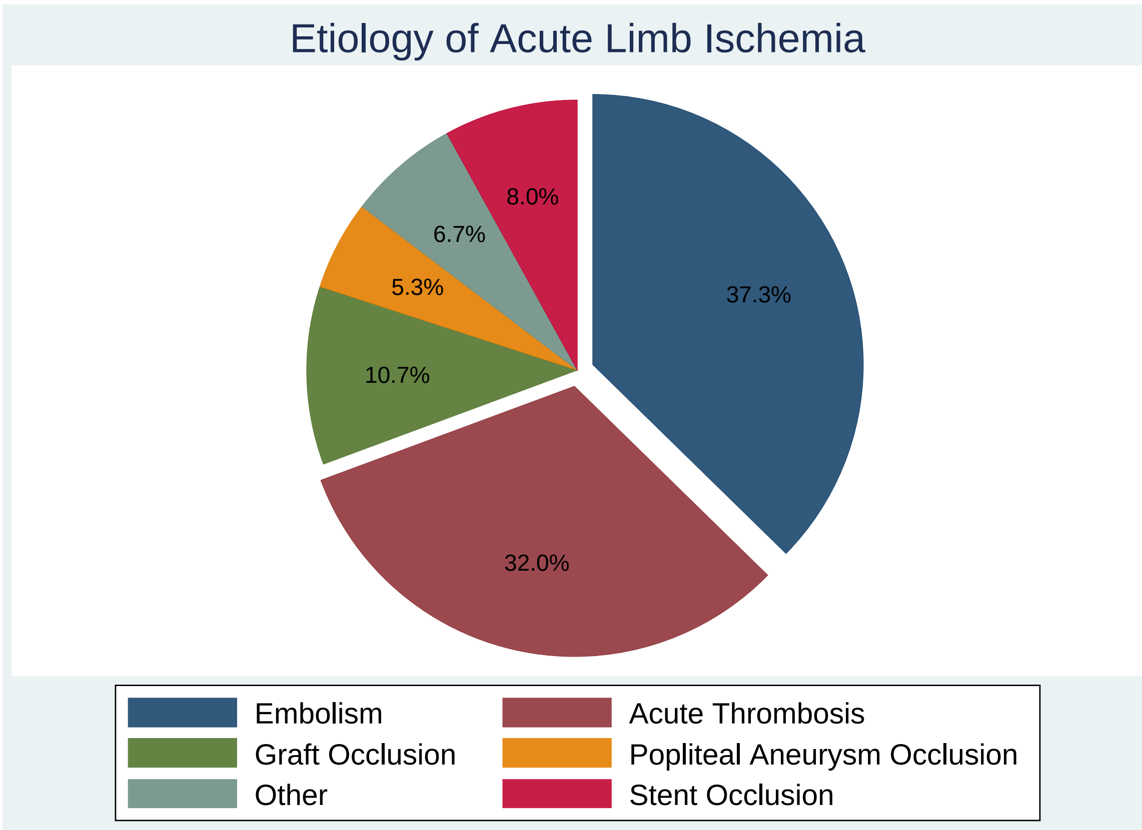


Figure 1. Etiology of acute limb ischemia. Embolism and in-situ thrombosis account for most peripheral artery occlusion.

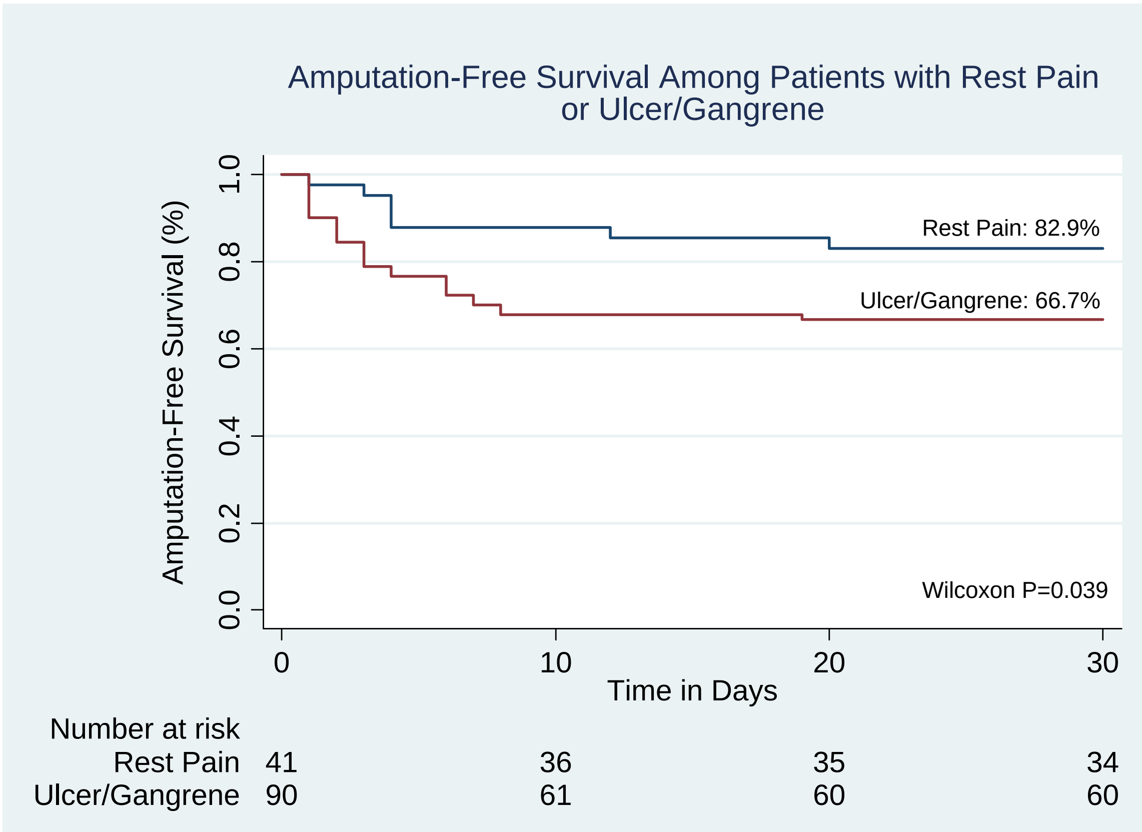


Figure 2. Amputation-free survival in rest pain and ulcer/gangrene.
Kaplan–Meier curves of 30-day amputation-free survival in CLI patients stratified by clinical presentation with rest pain or ulcer/gangrene. Presented are time in days on the horizontal axis and percent of amputation-free survival on the vertical axis.

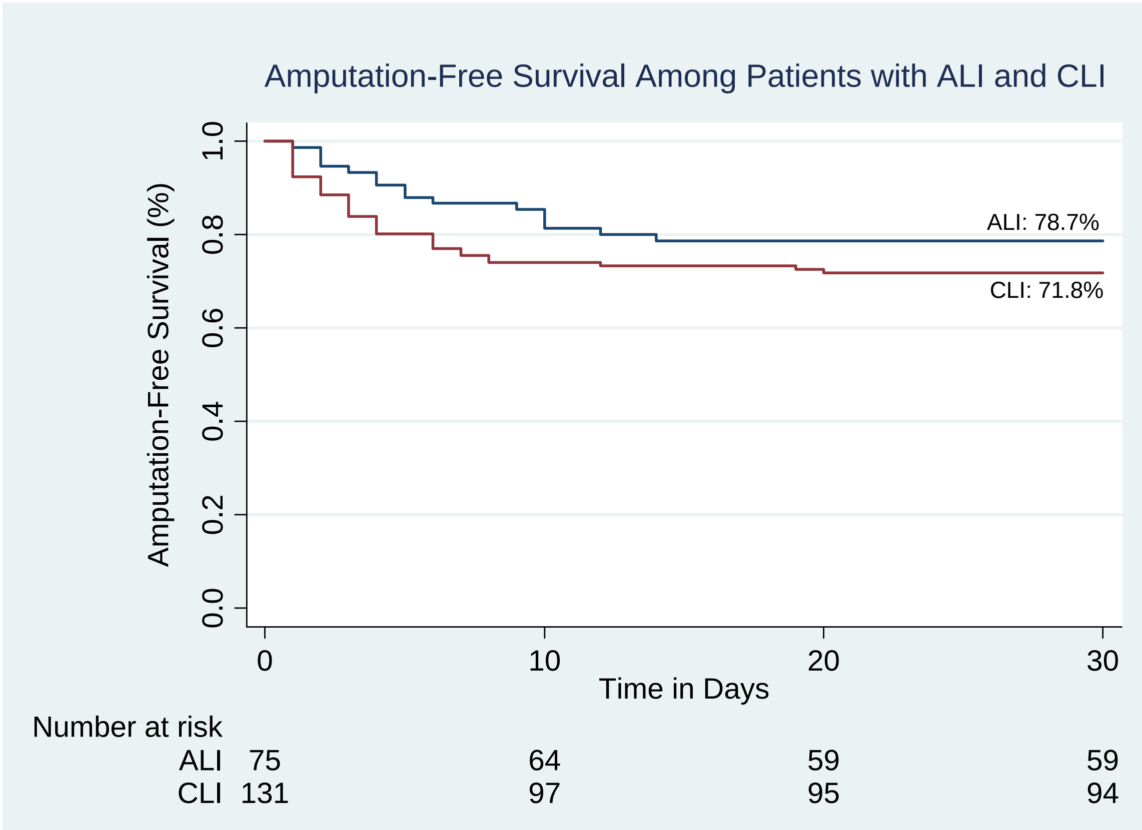
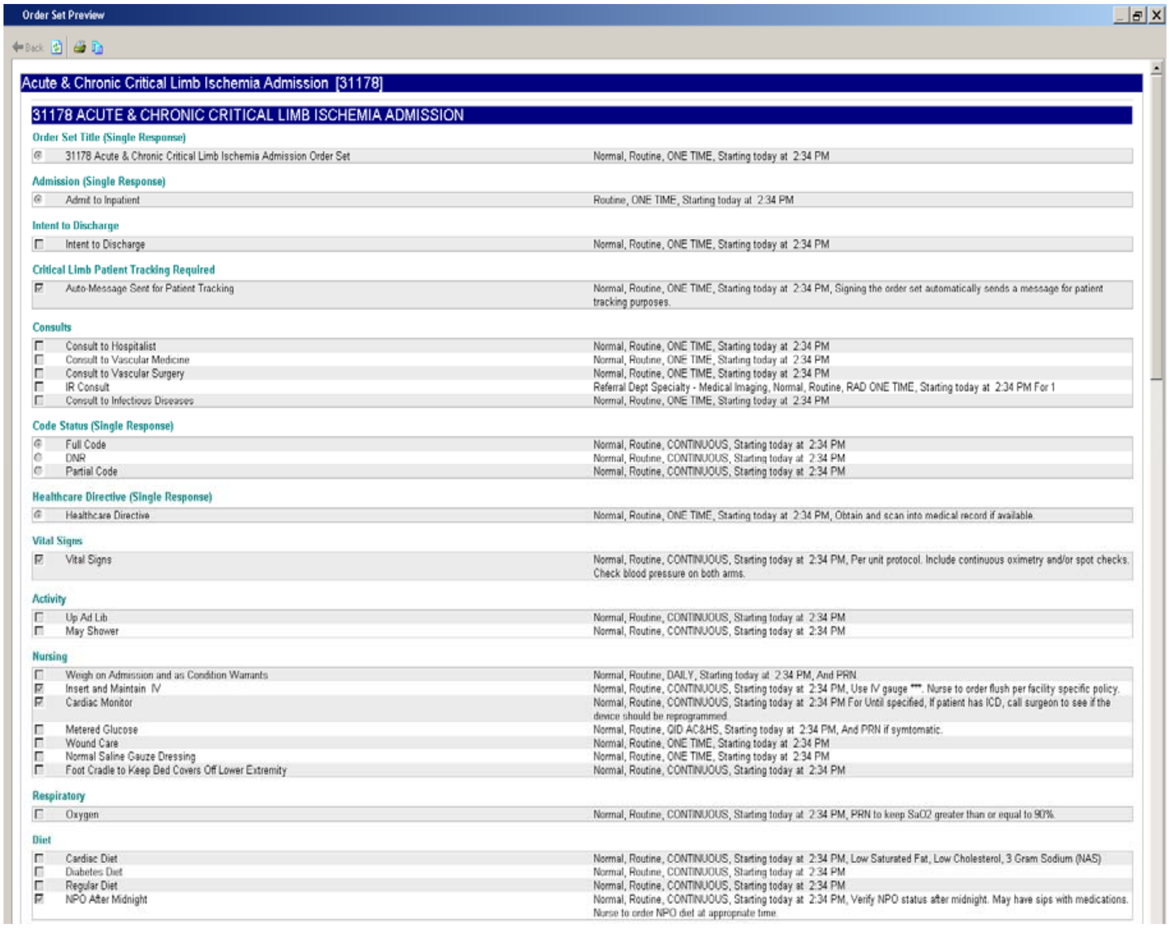


Figure 3. Amputation-free survival among ALI and CLI.

Kaplan–Meier curves of 30-day amputation-free survival stratified by acute or critical limb ischemia. ALI, acute limb ischemia; CLI, critical limb ischemia. Presented are time in days on the horizontal axis and percent of amputation-free survival on the vertical axis.

LIST OF APPENDICES

Appendix 1. Acute and chronic critical limb ischemia admission order set



Order Set Preview

Back

Acute & Chronic Critical Limb Ischemia Admission [31178]

31178 ACUTE & CHRONIC CRITICAL LIMB ISCHEMIA ADMISSION

Order Set Title (Single Response)

31178 Acute & Chronic Critical Limb Ischemia Admission Order Set	Normal, Routine, ONE TIME, Starting today at 2:34 PM

Admission (Single Response)

Admit to Inpatient	Routine, ONE TIME, Starting today at 2:34 PM

Intent to Discharge

Intent to Discharge	Normal, Routine, ONE TIME, Starting today at 2:34 PM

Critical Limb Patient Tracking Required

Auto-Message Sent for Patient Tracking	Normal, Routine, ONE TIME, Starting today at 2:34 PM, Signing the order set automatically sends a message for patient tracking purposes.

Consults

Consult to Hospitalist	Normal, Routine, ONE TIME, Starting today at 2:34 PM
Consult to Vascular Medicine	Normal, Routine, ONE TIME, Starting today at 2:34 PM
Consult to Vascular Surgery	Normal, Routine, ONE TIME, Starting today at 2:34 PM
IR Consult	Referral Dept Specialty - Medical Imaging, Normal, Routine, RAD ONE TIME, Starting today at 2:34 PM For 1
Consult to Infectious Diseases	Normal, Routine, ONE TIME, Starting today at 2:34 PM

Code Status (Single Response)

Full Code	Normal, Routine, CONTINUOUS, Starting today at 2:34 PM
DNR	Normal, Routine, CONTINUOUS, Starting today at 2:34 PM
Partial Code	Normal, Routine, CONTINUOUS, Starting today at 2:34 PM

Healthcare Directive (Single Response)

Healthcare Directive	Normal, Routine, ONE TIME, Starting today at 2:34 PM, Obtain and scan into medical record if available.

Vital Signs

Vital Signs	Normal, Routine, CONTINUOUS, Starting today at 2:34 PM, Per unit protocol. Include continuous oximetry and/or spot checks. Check blood pressure on both arms.

Activity

Up Ad Lib	Normal, Routine, CONTINUOUS, Starting today at 2:34 PM
May Shower	Normal, Routine, CONTINUOUS, Starting today at 2:34 PM

Nursing

Weigh on Admission and as Condition Warrants	Normal, Routine, DAILY, Starting today at 2:34 PM, And PRN
Insert and Maintain IV	Normal, Routine, CONTINUOUS, Starting today at 2:34 PM, Use IV gauge ***. Nurse to order flush per facility specific policy.
Cardiac Monitor	Normal, Routine, CONTINUOUS, Starting today at 2:34 PM For Until specified, If patient has ICD, call surgeon to see if the device should be reprogrammed
Metered Glucose	Normal, Routine, QID AC&HS, Starting today at 2:34 PM, And PRN if symtomatic.
Wound Care	Normal, Routine, ONE TIME, Starting today at 2:34 PM
Normal Saline Gauze Dressing	Normal, Routine, ONE TIME, Starting today at 2:34 PM
Foot Cradle to Keep Bed Covers Off Lower Extremity	Normal, Routine, CONTINUOUS, Starting today at 2:34 PM

Respiratory

Oxygen	Normal, Routine, CONTINUOUS, Starting today at 2:34 PM, PRN to keep SaO2 greater than or equal to 90%.

Diet

Cardiac Diet	Normal, Routine, CONTINUOUS, Starting today at 2:34 PM, Low Saturated Fat, Low Cholesterol, 3 Gram Sodium (NAS)
Diabetes Diet	Normal, Routine, CONTINUOUS, Starting today at 2:34 PM
Regular Diet	Normal, Routine, CONTINUOUS, Starting today at 2:34 PM
NPO After Midnight	Normal, Routine, CONTINUOUS, Starting today at 2:34 PM, Verify NPO status after midnight. May have sips with medications. Nurse to order NPO diet at appropriate time.

Medications

IV Fluids (Single Response)

NaCl 0.9% IV infusion 1000 mL	Intravenous, CONTINUOUS Starting today at 2:34 PM
select a different IV fluid	Intravenous, CONTINUOUS Starting today at 2:34 PM

Electrolyte Protocols

potassium replacement protocol	Protocol, PROTOCOL Starting today at 2:34 PM
magnesium replacement protocol	Protocol, PROTOCOL Starting today at 2:34 PM

Anticoagulation (Single Response)

heparin IV THERAPEUTIC protocol	Protocol, PROTOCOL Starting today at 2:34 PM
heparin Subcutaneous THERAPEUTIC protocol	Protocol, Q 12H Starting today at 2:34 PM
heparin IV PROPHYLACTIC Protocol	Protocol, PROTOCOL Starting today at 2:34 PM
heparin Subcutaneous PROPHYLACTIC Protocol	Protocol, Q 12H Starting today at 2:34 PM
enoxaparin (LOVENOX) THERAPEUTIC protocol	Protocol, Q 12H Starting today at 2:34 PM
enoxaparin (LOVENOX) PROPHYLACTIC Protocol	Protocol, Q 12H Starting today at 2:34 PM

Renal Insufficiency (Single Response)

acetylcysteine (MUCOMYST) 600 mg PO/NG - day of procedure dosing for patient ALREADY receiving 2 x 600 mg doses day prior to procedure.	600 mg, Oral/NG Tube, Q 12H Starting today at 2:34 PM For 2 Dose(s) Start day of procedure and give total of 2 doses. Give first dose now. Dilute acetylcysteine in 30 mL of soda or juice prior to administration and use within 1 hour of mixing. 600 mg = 3 mL of 20 % acetylcysteine solution. Routine
acetylcysteine (MUCOMYST) 1200 mg PO/NG - day of procedure dosing for patient NOT already receiving acetylcysteine (MUCOMYST)	1,200 mg, Oral/NG Tube, Q 12H Starting today at 2:34 PM For 2 Dose(s) Start day of procedure and give total of 2 doses. Give first dose now. Dilute acetylcysteine in 30 mL of soda or juice prior to administration and use within 1 hour of mixing. 1200 mg = 6 mL of 20% acetylcysteine solution. Routine

Oral Non-Narcotic Analgesic

acetaminophen (TYLENOL) PO/NG	650 mg, Oral/NG Tube, Q 3H PRN Starting today at 2:34 PM Maximum dose of acetaminophen is 4000 mg from all sources in 24 hours. Routine

Oral Narcotic Analgesics (Single Response)

oxyCODONE-acetaminophen (5-325 mg) (PERCOCET) PO/NG	1-2 tablet, Oral, Q 4H PRN Starting today at 2:34 PM, Routine
HYDROcodone-acetaminophen (5-500 mg) (VICODIN) PO/NG	1-2 tablet, Oral, Q 4H PRN Starting today at 2:34 PM, Routine

IV Narcotic Analagesic

morphine IV	1-4 mg, Intravenous, Q 2H PRN Starting today at 2:34 PM PRN for severe pain. Hold for respiratory rate less than 10 per minute. If pain not controlled at maximum dose call physician for further orders. Routine

Medications - Other

aspirin enteric coated 325 mg PO	325 mg, Oral, DAILY Starting today at 2:34 PM, Routine
nitroglycerin Sublingual	0.4 mg, Sublingual, Q 5MIN PRN Starting today at 2:34 PM Every 5 minutes x 3 doses. Hold for SBP less than 90. Routine
milk of magnesia PO/NG	30 mL, Oral/NG Tube, DAILY PRN Starting today at 2:34 PM, Routine
aluminum-magnesium hydroxides-simethicone (225-200-25 mg/5 mL) (MAALOX PLUS) PO/NG	30 mL, Oral/NG Tube, Q 2H PRN Starting today at 2:34 PM, Routine

Laboratory

Basic Metabolic Panel - In AM	Early AM, Normal, TOMORROW AM, Starting today at 2:34 PM For 1 Occurrences
Hepatic Function Panel	ASAP, Normal, ONE TIME, Starting today at 2:34 PM For 1 Occurrences
Lipid Panel Fasting	Early AM, Normal, TOMORROW AM, Starting today at 2:34 PM For 1 Occurrences
CBC and Differential	ASAP, Normal, ONE TIME, Starting today at 2:34 PM For 1 Occurrences
Protime - INR	ASAP, Normal, ONE TIME, Starting today at 2:34 PM For 1 Occurrences
Magnesium	ASAP, Normal, ONE TIME, Starting today at 2:34 PM For 1 Occurrences
Beta HCG Quant Pregnancy	ASAP, Normal, ONE TIME, Starting today at 2:34 PM For 1 Occurrences

Laboratory Hypercoagulation

Protein C	ASAP, Normal, ONE TIME, Starting today at 2:34 PM For 1 Occurrences
Protein S	ASAP, Normal, ONE TIME, Starting today at 2:34 PM For 1 Occurrences
Antithrombin III	ASAP, Normal, ONE TIME, Starting today at 2:34 PM For 1 Occurrences
Lupus Anticoagulants	ASAP, Normal, ONE TIME, Starting today at 2:34 PM For 1 Occurrences
Cardiolipin Antibody	ASAP, Normal, ONE TIME, Starting today at 2:34 PM For 1 Occurrences
Factor V Leiden	ASAP, Normal, ONE TIME, Starting today at 2:34 PM For 1 Occurrences
Factor II Gene Mutation	ASAP, Normal, ONE TIME, Starting today at 2:34 PM For 1 Occurrences
Homocysteine	ASAP, Normal, ONE TIME, Starting today at 2:34 PM For 1 Occurrences
Heparin Level	ASAP, Normal, ONE TIME, Starting today at 2:34 PM For 1 Occurrences
Type and Screen	Preop, Normal, PRN, Starting today at 2:34 PM For 1 , If not already completed. Nurse to release order.
Urinanalysis with Reflex Microsopic if Positivie	Routine, Unit Collect, ONE TIME, Starting today at 2:34 PM For 1 , Midstream.

Medical Imaging

Medical Imaging STAT

XR Chest PA and Lateral	Referral Dept Specialty - Medical Imaging, Normal, STAT, RAD ONE TIME, Starting today at 2:34 PM For 1 Occurrences, If not done in the last 6 months.
Ankle Brachial Index (ABI)	Referral Dept Specialty - Medical Imaging, Normal, STAT, RAD ONE TIME, Starting today at 2:34 PM For 1 Occurrences
Ankle Brachial Index (ABI) with Toe Brachial Index (TBI)	Referral Dept Specialty - Medical Imaging, Normal, STAT ... Starting today at 2:34 PM For 1 Occurrences, Include toe brachial index (TBI)
Aortoiliac Arterial Doppler Duplex	Referral Dept Specialty - Medical Imaging, Normal, STA ... Starting today at 2:34 PM For 1 Occurrences
Left Lower Extremity Arterial Doppler Duplex	Referral Dept Specialty - Medical Imaging, Normal, STA ... Starting today at 2:34 PM For 1 Occurrences
Right Lower Extremity Arterial Doppler Duplex	Referral Dept Specialty - Medical Imaging, Normal, STA ... Starting today at 2:34 PM For 1 Occurrences
Bilateral Lower Extremities Arterial Doppler Duplex	Referral Dept Specialty - Medical Imaging, Normal, STA ... Starting today at 2:34 PM For 1 Occurrences
CT Angio Left Lower Extremity	Referral Dept Specialty - Medical Imaging, Normal, STAT, RAD ONE TIME, Starting today at 2:34 PM For 1 Occurrences
CT Angio Right Lower Extremity	Referral Dept Specialty - Medical Imaging, Normal, STAT, RAD ONE TIME, Starting today at 2:34 PM For 1 Occurrences
MR Angio Bilateral Lower Extremities with Runoffs	Referral Dept Specialty - Medical Imaging, Normal, STAT, RAD ONE TIME, Starting today at 2:34 PM For 1 Occurrences

Medical Imaging Routine

XR Chest PA and Lateral	Referral Dept Specialty - Medical Imaging, Normal, Routine, RAD ONE TIME, Starting today at 2:34 PM For 1 Occurrences, If not done in the last 6 months
Ankle Brachial Index (ABI)	Referral Dept Specialty - Medical Imaging, Normal, Routine, RAD ONE TIME, Starting today at 2:34 PM For 1 Occurrences
Ankle Brachial Index (ABI) with Toe Brachial Index (TBI)	Referral Dept Specialty - Medical Imaging, Normal, Routine, RAD ONE TIME, Starting today at 2:34 PM For 1 Occurrences, Include toe brachial index (TBI)
Aortoiliac Arterial Doppler Duplex	Referral Dept Specialty - Medical Imaging, Normal, Routine, RAD ONE TIME, Starting today at 2:34 PM For 1 Occurrences
Left Lower Extremity Arterial Doppler Duplex	Referral Dept Specialty - Medical Imaging, Normal, Routine, RAD ONE TIME, Starting today at 2:34 PM For 1 Occurrences
Right Lower Extremity Arterial Doppler Duplex	Referral Dept Specialty - Medical Imaging, Normal, Routine, RAD ONE TIME, Starting today at 2:34 PM For 1 Occurrences
Bilateral Lower Extremity Arterial Doppler Duplex	Referral Dept Specialty - Medical Imaging, Normal, Routine, RAD ONE TIME, Starting today at 2:34 PM For 1 Occurrences
CT Angio Left Lower Extremity	Referral Dept Specialty - Medical Imaging, Normal, Routine, RAD ONE TIME, Starting today at 2:34 PM For 1 Occurrences
CT Angio Right Lower Extremity	Referral Dept Specialty - Medical Imaging, Normal, Routine, RAD ONE TIME, Starting today at 2:34 PM For 1 Occurrences
MR Angio Bilateral Lower Extremities with Runoffs	Referral Dept Specialty - Medical Imaging, Normal, Routine, RAD ONE TIME, Starting today at 2:34 PM For 1 Occurrences

EKG

EKG

EKG 12 Lead	Normal, Preop, PRN, Starting today at 2:34 PM For 1 Occurrences, If not already completed. For preop evaluation unless done within 7 days. Nurse to release order.

Interdisciplinary Consults

Interdisciplinary Consults

Wound Ostomy Evaluate and Treat	Normal, Routine, ONE TIME, Starting today at 2:34 PM
Consult to Tobacco Cessation	Normal, Routine, PRN, Starting today at 2:34 PM For 1 Occurrences, If patient smokes. Nurse to release.
Consult to Social Service	Normal, Routine, ONE TIME, Starting today at 2:34 PM

Close

Appendix 2. Acute and chronic critical limb ischemia discharge order set

Order Set Preview

DC Critical Limb Ischemia [31213]

31213 DC Critical Limb Ischemia

Order Set Title

31213 DC Critical Limb Ischemia	Normal, Routine, ONE TIME, Starting today at 2:44 PM

Discharge

Discharge to Home Self Care	Normal, Routine, ONE TIME, Starting today at 2:44 PM
Discharge to:	Normal, Routine, ONE TIME, Starting today at 2:44 PM

Discharge Advanced Care Planning

AMB Consult for Advanced Care Planning	Expires: 4/27/11, Routine, Referral, Allina Care Navigation to provide follow up for Advanced Care Planning.

Nursing Discharge

Provide warfarin (COUMADIN) Patient Teaching Prior to Discharge	Normal, Routine, CONTINUOUS, Starting today at 2:44 PM
Tobacco Cessation	Normal, Routine, ONE TIME, Starting today at 2:44 PM, Nurse to verify that tobacco education materials have been given to patient prior to discharge.

Primary Care Physician

Change Primary Care Physician	Normal, Routine, ONE TIME, Starting today at 2:44 PM

After Discharge Orders

Patient Discharge Instructions - Activity

Activity: As Tolerated	Routine, Clinic Performed
Activity: No Restrictions	Routine, Clinic Performed
Activity: Per Rehab Recommendations	Routine, Clinic Performed
Activity (Specify)	Routine, Clinic Performed, ***.
No Weight Bearing on Affected Limb	Routine, Clinic Performed, For ***.

Restrictions post Angiography

Do NOT lift more than 10 pounds for 2 days	Routine, Clinic Performed
Do NOT drive for 3 days	Routine, Clinic Performed

Wound care

Sutures / Staples: Remove 2 weeks from day of surgery	Routine, Clinic Performed
Steri-strips: Leave intact until 3 weeks post-op and replace as needed	Routine, Clinic Performed
Change dressing daily	Routine, Clinic Performed
Cover wound as desired or if drainage present	Routine, Clinic Performed
Document wound drainage (amount, color, odor) and notify MD if suspect infection.	Routine, Clinic Performed
May shower with waterproof dressing over sutures / staples	Routine, Clinic Performed
Wound Care: Specify	Routine, Clinic Performed
Follow Wound Care Nurse Specialist Instructions.	Routine, Clinic Performed

Other Discharge Instructions

Other Discharge Instructions	Routine, Clinic Performed

Diet (Single Response)

Diet: Regular	Routine, Clinic Performed
Diet: Diabetic	Routine, Clinic Performed
Diet: Low Cholesterol / Low Fat	Routine, Clinic Performed
Diet: As Tolerated	Routine, Clinic Performed
Diet: Specify	Routine, Clinic Performed, ***.

Follow Up with Physician:

Follow Up with Primary Doctor (Specify)	Routine, Clinic Performed, ***.
Follow Up with Vascular Surgeon (Specify)	Routine, Clinic Performed, ***.
Follow Up with Radiologist (Specify)	Routine, Clinic Performed, ***.
Follow Up with Cardiologist (Vascular Medicine)	Routine, Clinic Performed, In *** week(s).
OP Consult to Wound Clinic	Routine, Hospital Performed
AMB Consult to Podiatry	Expires: 4/27/11, Routine, Referral
AMB Consult to Pain Clinic	Expires: 4/27/11, Routine, Referral

Follow Up Vascular Study - 3 Months

US Ankle Brachial Index - Exercise - 3 Months	Expected:7/11/10, Expires: 8/20/10, Routine, Normal
US Ankle Brachial Index - Resting - 3 Months	Expected:7/11/10, Expires: 8/20/10, Routine, Normal
US Arterial Duplex Lower Ext Bilateral - In 3 Months	Expected:7/11/10, Expires: 8/20/10, Routine, Normal

Follow Up Vascular Study - 6 Months

US Ankle Brachial Index - Exercise - 6 Months	Expected:10/9/10, Expires: 11/8/10, Routine, Normal
US Ankle Brachial Index - Resting - 6 Months	Expected:10/9/10, Expires: 11/8/10, Routine, Normal
US Arterial Duplex Lower Ext Bilateral - In 6 Months	Expected:10/9/10, Expires: 11/8/10, Routine, Normal

Follow Up Vascular Study - 9 Months

US Ankle Brachial Index - Exercise - 9 Months	Expected:1/7/11, Expires: 2/6/11, Routine, Normal
US Ankle Brachial Index - Resting - 9 Months	Expected:1/7/11, Expires: 2/6/11, Routine, Normal
US Arterial Duplex Lower Ext Bilateral - In 9 Months	Expected:1/7/11, Expires: 2/6/11, Routine, Normal

Follow Up Vascular Study - 1 Year

US Ankle Brachial Index - Exercise - 1 Year	Expected:4/12/11, Expires: 4/27/11, Routine, Normal
US Ankle Brachial Index - Resting - 1 Year	Expected:4/12/11, Expires: 4/27/11, Routine, Normal
US Arterial Duplex Lower Ext Bilateral - In 1 Year	Expected:4/12/11, Expires: 4/27/11, Routine, Normal

Future Labs

Basic Metabolic Panel 1 Week after Discharge	Expected:4/27/10, Expires: 7/26/10, Routine, AML Run/Clinic Bill
Hepatic Function Panel 8 Weeks after Discharge	Expected:4/27/10, Expires: 7/26/10, Routine, AML Run/Clinic Bill
Lipid Panel 8 Weeks after Discharge	Expected:4/27/10, Expires: 7/26/10, Routine, AML Run/Clinic Bill

Discharge Prescriptions - Pain (Single Response)

oxyCODONE-acetaminophen (5-325 mg) (PERCOCET), 1-2 tablets PO	30 tablet, 0, starting 4/27/10, Normal
HYDROcodone-acetaminophen (5-500 mg) (VICODIN), 1-2 tablets PO	30 tablet, 0, starting 4/27/10, Normal

Discharge Prescriptions - Antiplatelet

Aspirin 81 mg tablet PO	30 tablet, 0, starting 4/27/10, Normal
Aspirin 325 mg tablet PO	30 tablet, 0, starting 4/27/10, Normal
clopidogrel (PLAVIX) 75 mg tablet PO	30 tablet, 0, starting 4/27/10, Normal

Discharge Prescriptions - Lipid Lowering Agents (Single Response)

simvastatin (ZOCOR) 10 mg tablet PO	30 tablet, 0, starting 4/27/10, Normal
simvastatin (ZOCOR) 20 mg tablet PO	30 tablet, 0, starting 4/27/10, Normal
simvastatin (ZOCOR) 40 mg tablet PO	30 tablet, 0, starting 4/27/10, Normal
atorvastatin (LIPITOR) 10 mg tablet PO	30 tablet, 0, starting 4/27/10, Normal
atorvastatin (LIPITOR) 20 mg tablet PO	30 tablet, 0, starting 4/27/10, Normal
atorvastatin (LIPITOR) 40 mg tablet PO	30 tablet, 0, starting 4/27/10, Normal

Close

Appendix 3. Standardized transfer orders

ABBOTT NORTHWESERN'S VASCULAR CENTER

ACUTE CRITICAL LIMB ISCHEMIA TRANSFER ORDERS

Height/Weight: ____________ Allergies: ____

1. Admitting diagnosis ____

2. Transfer to: Abbott Northwestern Hospital

3. Code status: ___Full Code with ACLS protocol ___DNR ___DNI ___Health Care Directive

4. Diagnostic tests:
   ___Lower Extremity Arterial Duplex (3127)
   and Bilateral Ankle-Brachial Index/ Toe-Brachial Index (3208)
   ___ STAT (acute CLI) ___ same day (chronic CLI)
   ___Aortoiliac arterial duplex (3025)
   INDICATION: ____

6. Routine Labs:
   ___ Basic Metabolic Panel ___ Beta HCG
   ___ CBC w platelets, Diff
   ___ PT/INR (487)

7. ___Chest X-ray PA & Lateral (within last 6 months).

8. ___12 lead EKG (within 7 days).

13. ORAL MEDICATIONS: Please use order sheet if more space is needed.
    a. aspirin 325 mg PO daily
    b. Other ____

14. HEPARIN
    ___ Heparin IV therapeutic protocol with loading dose (60 units/kg/hr [4,000 units max] followed by continuous infusion at 12 unites/kg/hr [1,000 units max])

15. ANALGESICS/NARCOTICS
    ___acetaminophen 650 mg PO q 3h prn
    ___Morphine Sulphate 1-5mg IV q2-6h prn

18. NPO except for meds with sip of water.

19. IV: Normal Saline at ________ mL/h (#20 or 18 Jelco) CV Lab

21. ____

page 1/1 ________________________________ M.D.

Outreach hospital Name

Patient Name ____

Social Security # ________________________ Date of Birth ____________

Date of Surgery/Admission ____

PHYSICIAN'S ORDERS

PHYSICIAN'S ORDERS

Appendix 4. Dictation template

Standard Template

Acute Limb Ischemia-Critical limb Ischemia

History and Physical Admission or Consult Note

For every patient admitted to Abbott Northwestern Hospital with ALI or CLI that will be entered into our QA database, it is imperative that the initial vascular specialty H&P or consultation note include the following fields:

Demographics:

Age, gender

Primary care physician, referring physician, and referral hospital or clinic

Admitted from home or long-term care facility

Employment status (FT, PT, retired, unemployed, unable to work)

Highest level of education completed (1-8 grade, 9-12 grade, technical/trade school, college/university)

Social History:

(a) Smoking history, pack/days
(b) Family history of CAD (age <55 years)

Medical History:

History of PAD:

(a) Past history of claudication

(b) Past history of ALI or CLI (when? How cared for?)

(c) Past endovascular or open surgical procedures (specify type and date)

(d) History of CAD, hypertension, PCI, MI, CABG

(e) History of TIA, stroke, CEA, carotid stenting

(f) Known prothrombotic disorder

History of Present Illness-Current ALI-CLI History:

(a) Duration and specifics of current ischemic event: Narrative history

(b) Precise onset of initial ALI-CLI symptoms. Give time frame in:

-- minutes for onset < 48 hr

-- hours for onset 48-72 hrs

-- days for onset of 3 days to 30 days

-- weeks for onset > one month

(c) If CLI, describe presence or absence of ischemic rest pain, non-healing wound or gangrene

(d) If ALI, describe onset and present of "5 P"s (pain, pulselessness, pallor, paresthesia, poikilothermy), and presence of wounds, motor or sensory deficit

ALI-CLI Diagnostic Confirmation:

(a) What immediate objective diagnostic tests have been performed to establish the diagnosis?:

ABI or TBI or TCPO2

NOTE!: Without one of these tests, the ALI-CLI dx is not established!

b) What other supportive vascular anatomic imaging studies have been performed?

Arterial duplex, MRA, CTA or angiography

(c) What other diagnostic tests were performed?:

CBC, BMP, ECG, echocardiogram, hypercoagulable evaluation

Initial ALI-CLI Therapies Already Given:

Heparin, ASA, clopidogrel, antibiotics

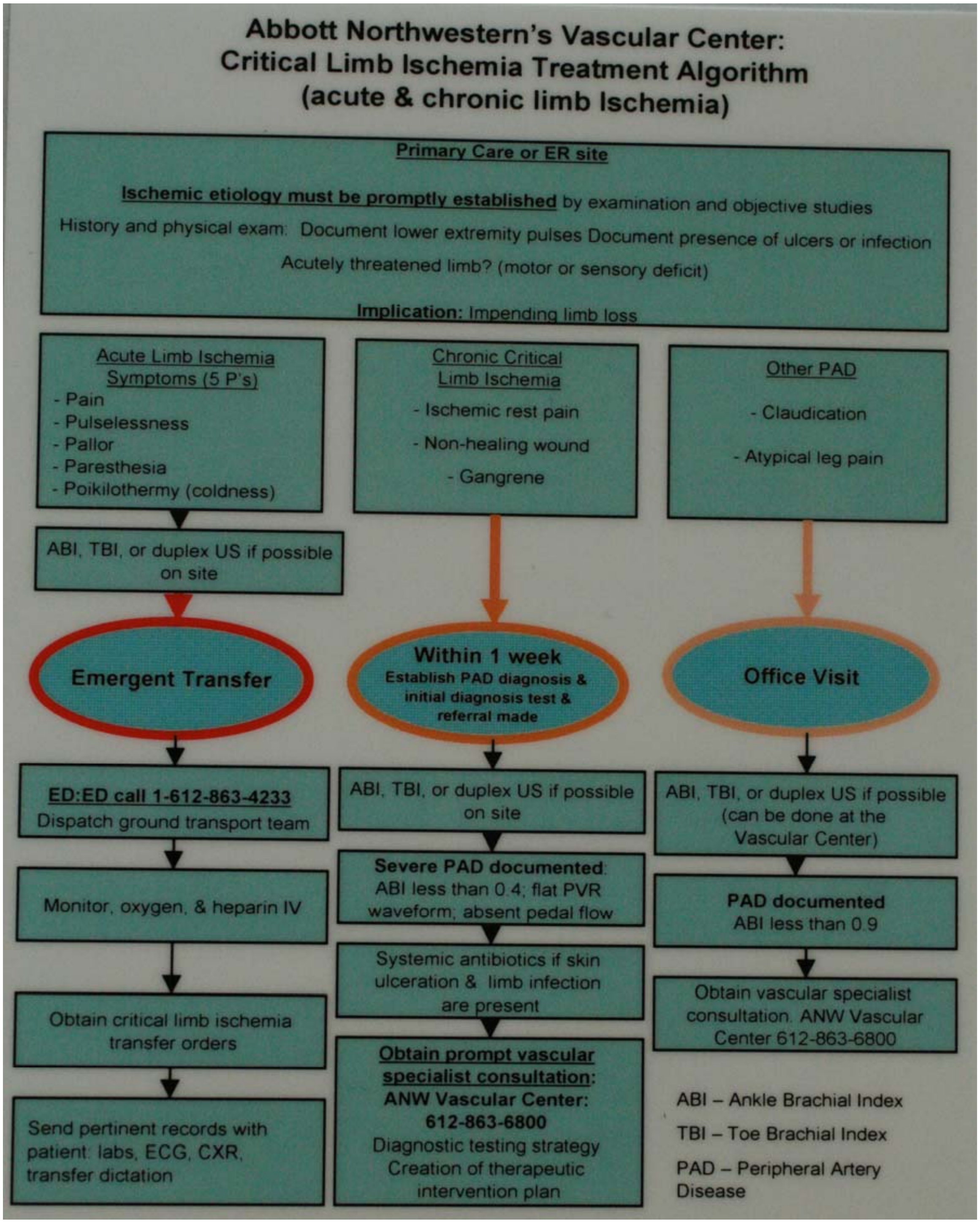
General and Vascular Physical Examination:

Full exam including cardiac rhythm, pulse exam, warmth, CMS (circulation, motor, sensory). Pulse exam should be 0 (absent), 1 (diminished), 2 (normal), 3 (bounding).

Final Vascular Diagnostic Impression and Care Plan:

Please be sure to define and state: Acute vs. chronic critical limb ischemia

Appendix 5. Acute and chronic critical limb ischemia treatment algorithm



Appendix 6. ALI/CLI-specific written health care plan

Abbott Northwestern's Vascular Center Critical Limb Ischemia Program

"Save a Leg, Save a Life"

Dear Patient, Spouse, and Family:

We are pleased that we have been able to participate in care that we hope will help you preserve your vascular and overall health. As you return home, it is important that your healthcare team, including your primary care clinician and vascular specialist, and many other clinicians (podiatrists, wound nurses, cardiologists, endocrinologists, and others) remain in close communication to protect your health.

You have been treated for "critical limb ischemia" (or simply, "CLI"). Critical limb ischemia is defined by the symptoms that occur when leg artery blood flow is severely decreased by peripheral arterial disease, or "P.A.D.". All patients who have been treated for CLI should receive lifelong monitoring and treatment of their P.A.D., as the risk of both leg symptoms (pain, wounds, or amputation) and of heart attack, stroke, or death continue.

These risks, once recognized, can be minimized with care. This page is intended to help empower you to lower your health risks.

Take care of your feet:

1 You should inspect your feet daily to be sure that there are no cuts, sores, or wounds. If you do note such sores, be sure to bring these to the attention of your primary care physician, podiatrist, or vascular specialist.

2 Avoid any accidents that might injure your feet! Never walk barefoot. Do not expose your feet to sharp objects. Use well-fitting footwear and avoid callous

formation. Do not cut your toenails too short. Be sure to inform any other healthcare providers or podiatrists from whom you seek care that you have been treated for P.A.D. and CLI.

3 If you were treated by surgical placement of a vascular surgical bypass graft, be certain to discuss with your vascular specialist the schedule of arterial "duplex ultrasound" studies that should be used to assure that this graft remains open. If narrowings are observed, even in the absence of symptoms, you may require treatment to help keep this graft open. Such ultrasound studies are usually performed approximately 3, 6, and 12 months, and then yearly after graft placement.

4 If you have been treated for a foot wound, be sure to follow the wound care instructions carefully, and keep all appointments with the wound clinic or podiatrist.

5 If you have had P.A.D.-related foot pain, be sure to understand the use of any prescribed pain medications.

6 Review your doctor's prescription of activity. While you may be advised to stay off your feet for a time period after treatment, staying as active as you can is important to your overall health, strength, and mood.

Take care of your heart and mind:

1 You should be familiar with the risk factors that caused your P.A.D. and the specific treatment goals that you should achieve. These goals should be achieved immediately and this treatment sustained for life.

2 If you smoke, stop smoking immediately. Ongoing smoking is the most potent factor that worsens the blockages from P.A.D., will block any new angioplasty or surgical bypasses, is a major cause of foot pain, amputation, heart attack and death. There are effective treatments to help you quit and patients with P.A.D. who smoke can successfully quit smoking. All forms of tobacco (including snuff and chewing tobacco) are equally dangerous.

3 Take all of your medications daily. Most individuals with P.A.D. will be treated with aspirin (either 81 or 325 mg, and both are effective). Some individuals may be prescribed a similar medication called clopidogrel (or Plavix®) for either a limited period of time or for life. Discuss which medications you need before you are discharged.

4 If you have P.A.D, your blood cholesterol levels are extremely important and must be lowered right away with either diet or medications, or both. Your LDL (bad) cholesterol should be less than 100 mg/dl. For some patients, this value should be less than 70 mg/dl. Know your LDL cholesterol numbers!

5 If you have high blood pressure (hypertension), you are at increased risk of heart attack, stroke, heart failure, kidney damage, or worsened P.A.D. Your blood pressure should stay below 140/90 mmHg or, if you have diabetes, stay below 130/80 mmHg. You should monitor this either by visiting your doctor or by using a home blood pressure cuff.

6 If you have diabetes, work with your doctor to lower your A1c values to less than 7.0%. If you have neuropathy, foot inspection is especially important.

These instructions are based on proven knowledge and, if followed carefully, can help you "save your legs and save your life". When such care plans are followed, health and independence are best sustained.

Please be sure to ask any questions. We would be pleased to remain your partner in sustaining your health and well-being.