# Diagnosis and treatment of Acute Lower Limb Ischemia and its effect on treatment results

Master Thesis in Medicine

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## Abstract

***Objective***

Acute Lower Limb Ischemia (ALLI) is a serious condition where an artery of the lower limb is occluded resulting in impaired blood flow. The condition may lead to death and amputation and require urgent medical care.

***Aim***

The purpose of this study was to describe the early chain of care of ALLI patients with particular emphasis on early detection and the use of Emergency Medical Services (EMS) as well as administration of Low Molecular Weight Heparin (LMWH).

***Methods***

The study included 108 patients for whom medical records at the Sahlgrenska University Hospital were reviewed. All patients treated with a main diagnosis of I74.3 according to ICD-10 fulfilled inclusion criteria.

***Results***

Patients transported to the Emergency Department (ED) by EMS differed from those who were not in several ways. They were 8.5 years older. A history of congestive heart failure and atrial fibrillation/flutter was more frequent among those who used EMS whereas the opposite was found with regard to previous Peripheral Arterial Disease (PAD).

The median time from hospital arrival to first physician contact was 52 minutes when ALLI was suspected by the EMS personnel and 102 minutes if not (p=0.017). The time from symptom onset to revascularization was shorter when the EMS personnel suspected ALLI, 17 hours compared to 56 hours when not (p=0.011). Administration of LMWH in the ED tended to be associated with improved outcome.

***Conclusion***

Patients who use EMS were older and had a more severe co-morbidity than those who did not. Early detection of ALLI by the EMS personnel was associated with a shorter delay to see a physician and to revascularization. Early treatment with LMWH might be associated with improved outcome.

## Introduction

### *Background*

Acute Lower Limb Ischemia (ALLI) is a form of Peripheral Arterial Disease (PAD) that requires immediate medical attention. Other forms of PAD are Intermittent Claudication (IC), and Critical Limb Ischemia (CLI). PAD is very common, particularly in the elder population. [1].

When present, ALLI is a serious medical condition resulting in chronic damage to the affected limb or amputation. ALLI is defined as an urgent loss of blood circulation in the lower extremity, resulting in threatened limb viability[1].

### *Pathophysiology and etiology*

Acute lower limb ischemia has several etiologies. The most common etiologies are; thrombosis in situ in the affected artery [2], embolism originating from the heart [3] or dissection or trauma. The clinical consequence is an occluded artery, resulting in reduced or depleted blood circulation in the affected extremity [3]. Thrombosis is commonly formed arterial segments with pre-existing atherosclerotic plaques, leading to a sudden worsening of an already present PAD, often referred to as Acute-On-Chronic (AoC). Thrombosis may also occur in previous arterial reconstructions, in arterio-venous malformations, and in popliteal aneurysms. Atrial flutter or atrial fibrillation is the main cause to cardiac embolisms. In these cases the thrombus is commonly formed in the auricles of the heart, travelling along the bloodstream as an embolus until the lumen narrows and the embolus occludes the vessel. Another reason for cardiac embolism is a recent myocardial infarction, where the hypokinetic myocardium allows for blood congestion and embolism formation [4]. A less common genesis for embolism is atrial myxoma and paradoxal embolism[5, 6].

Ischemia is a biochemical reaction due to absence of oxygen. As a consequence of oxygen deficit, anaerobic metabolism is commenced in the cells of the affected tissue. Lactic acid is produced by anaerobic metabolism and due to failing ATP-reliant ion transport pumps calcium accumulates in the cell. High intracellular calcium levels generate phospholipases and other enzymes degrading the cell components. As the cell membrane is damaged by the release of phospholipases more cytotoxic substances enter the cell and the mitochondria deteriorate, leading to apoptosis of the cell. If apoptosis is not present the cell may also necrotize [7, 8].

As an effect of ischemia an imminent immune response will be present, causing a major inflammatory reaction in the hypoperfused tissue. Cytokines and other metabolites released from the necrotic cells attract inflammatory cells to the location of the ischemic reaction. An adverse effect of the inflammatory response is edema, which in severe cases result in increased pressure within one or several compartments of the limb. The increased interstitial pressure leads to a further lowered capillary perfusion of the tissue, and thereby increased ischemia. This condition is referred to as compartment syndrome and needs immediate fasciotomy to release pressure [8-10]. In severe cases rhabdomyolysis may occur leading to kidney failure due to high blood levels of myoglobin, a remnant of shattered muscle cells [11]. Compartment syndrome is common after reperfusion in severe limb ischemia and is then referred to as reperfusion syndrome [12].

***Epidemiology and risk factors***

There is very little consistent data available regarding the frequency of ALLI. ALLI has been reported to be a rather rare condition, and different data sources report various incidence and prevalence. However, previous studies have shown that approximately 14/100 000 are affected by Acute Lower Limb Ischemia yearly [1]. The National Registry for Vascular

Surgery reported 820 revascularization procedures for ALLI during 2013[13]. The reported incidence of other forms of PAD differs substantially between studies. In a population in the age of 55 and above, 16 % of individuals suffered from any form of PAD in the lower extremities. A German study has shown that 19.8 % in a male population suffered from PAD. A Swedish study has shown that 4.1 % of individuals aged 50-89 suffered from a symptomatic chronic PAD in the lower extremities [14]. The most recently reported Swedish data states that almost one fifth of individuals >60 years of age suffers from any sort of PAD [15].

As atherosclerosis is a main cause of ALLI, as well as cardiovascular disease and cerebrovascular disease these conditions share other risk factors as well. Common risk factors for PAD and ALLI are hence diabetes mellitus, smoking, hyperlipidemia, hypertension, kidney disease and a previous cardiovascular or cerebrovascular disease [14]. The risk of an embolic event is markedly increased by atrial flutter/fibrillation, recent myocardial infarction, previous stroke and previous ALLI [1]. According to a study performed in Edinburgh smokers have a 3.7 times increased risk of PAD compared to non smokers [16]. 50-80 % of patients with PAD suffer from hypertension according to several studies [14]. A British study (UKPDS) performed on 3834 individuals without PAD at the time of diagnosis of diabetes mellitus type 2 proposed that an increase of HbA1c of 1 % (11 mmol/mol) leads to an increased risk of 28 % to develop PAD in the lower extremities [17]. Patients developing PAD often suffer from several of the risk factors mentioned above [18].

***Clinical presentation***

ALLI has a varying clinical presentation depending on etiology, severity and progress of the process. ALLI of embolic genesis commonly presents as a pale, painful and numb extremity [19]. The debut is often sudden, and patients can remember the time of onset very accurately.

There are several clinical symptoms coherent with ALLI. A common presentation of symptoms is referred to as "The six P's", denoting Pain, Pallor, Paresthesia, Poikilothermia, Pulselessness, and Paralysis [3, 10]. Patients have a lowered Ankle-Brachial Index (ABI), a simple examination indicating a lowered blood pressure in the affected limb due to arterial obstruction [20]. In certain cases the syndrome is presented only by paralysis and numbness in the affected limb and may therefore be incorrectly diagnosed as cerebrovascular or spinal disease [21]. In some cases cyanosis may be present. For patients with thrombosis in situ the progress is slower and more sub-acute. Among these patients, it is common with paresthesia and intact motor function and they do not commonly present with all six P's [3].

**Figure 1** - SVS/ISCVS acute limb ischemia classification.

| Category | Prosnosis | Sensory | Motor | Arterial Doppler | Venous Doppler |
|---|---|---|---|---|---|
| I: Viable | No immediate threat | None | None | Audible | Audible |
| IIA: marginally threatened | Salvagable if properly treated | Minimal or none | None | Inaudible | Audible |
| IIB: Immidiately threatened | Salvagable if immediately recascularized | Rest pain | Mild/ moderate | Inaudible | Audible |
| III: Irriversible | Major tissue loss, permanent nerve damage inevitable | Profound, anaesthetic | Profound, paralysis (rigor) | Inaudible | Audible |
| Rutherford, R.B., et al., *Recommended standards for reports dealing with lower extremity ischemia: revised version.* J Vasc Surg, 1997. **26**(3): p. 517-38. | | | | | |

A clinical scale for classification is proposed in 1997, known as the SVS/ISCVS (Society of Vascular Surgery/International Society of Cardiovascular Surgery) acute limb ischemia classification, fig. 1, is used in clinical practice [22]. The scale consists of four steps assessing the risk of limb damage and thereby need of acute medical care. Class I is a viable limb with no signs of, or symptoms such as motor or sensory loss. Class II consists of two grades, class IIA, which is a marginally threatened limb showing mild symptoms, and class IIB which is an immediately threatened limb showing a higher grade of symptoms. Class III indicates a limb with major symptoms, such as motor and sensory loss. In a Class III limb the ischemic process has resulted in irreversible damage to the affected limb [22].

### *Treatment and prognosis*

At the emergency department (ED) administration of Low Molecular Weight Heparin (LMWH) may prevent further propagation of the thrombus, and a rapid diagnosis is important to ensure a good treatment result of surgery [10]. There are two major revascularization interventions clinically used: catheter-directed thrombolysis and surgery [23]. Thrombolysis is performed by intravasal administration of a tissue plasminogen activator, alteplase (rTPA) [24]. The intervention is performed by using endovascular techniques to place a catheter within the occlusion and at this site administer rTPA. Normally the catheter is inserted into the vessel via the femoral artery on the contralateral side but this depends on the location of the thrombus in the extremity[25, 26]. Surgical thrombembolectomy is normally performed by using a Fogarty balloon catheter. Following a surgical cut-down and arterial cross-clamping the artery is entered proximally to the obstruction, commonly in the femoral artery [27]. Removal of the thrombus is done by passing the arterial obstruction with the catheter and inflating the balloon at the tip of the catheter distally to the thrombus. The balloon is inflated until filling the lumen of the vessel. The balloon is then drawn in proximal direction along the artery, bringing the thrombus to the location of the arterial incision and making an extraction possible. After the thrombus is removed the artery is sutured and blood flow is reestablished [1, 10]. The procedure can be performed during local anesthesia. In some cases more extensive vascular procedures, such as bypass surgery, is performed [1]. According to the STILE-study there was no significant difference between catheter-directed thrombolysis and thrombembolectomy in 30-day survival. In patients with ALLI thrombolysis has been reported to have a significantly higher amputation-free survival compared to surgical treatment, but no significant difference in several other parameters analyzed [24]. Similar results was found in a recent Cochrane report describing no significant differences regarding outcome between the interventions [28]. Thereby it may be stated that the prognosis is more dependent on the severity and classification of the ischemia rather than choice of intervention [1, 24].

**Aim**

ALLI is a very serious condition with a high rate of amputation and death among patients. Many factors may affect the outcome of treatment in emergency care, and not much research has been done on this area. The purpose of the survey was to study the patients who had been diagnosed with ALLI and who had undergone thrombolysis, revascularization surgery or other treatment. The aim was to describe the early chain of care with emphasis on early detection, the usage of EMS and early use of LMWH. The following research questions were formulated:

1. What factors in the early chain of care may affect survival and rate of amputation among patients affected by ALLI?
2. Will early administration of LMWH affect patient outcome regarding death and amputation in patients affected by ALLI?

## Material and methods

### *Study design*

The study was a retrospective descriptive cohort study conducted on hospital records for patients with a defined main diagnosis of I74.3 according to the International Classification of Diseases, 10$^{th}$ revision (ICD-10).

### *Time of survey*

The study was conducted on patient records from 2012-01-01 to 2014-12-31. The study was conducted in Sept 2015 to Nov 2015.

### *Study area*

The study was conducted at Sahlgrenska University Hospital (SU) in Gothenburg and Mölndal municipality, Sweden. Sahlgrenska University Hospital consists of three different emergency wards, located at SU/Östra, SU/Mölndal and SU/Sahlgrenska. The cardiovascular surgery department is located in SU/Sahlgrenska and patients are therefore transported to this hospital if invasive interventions are indicated. The Sahlgrenska University Hospital serves approximately one million inhabitants in the Gothenburg Region, and serves up to 1.7 million people as being the tertiary referral hospital of Western Sweden.

### *Inclusion*

Patients were eligible for the study if they;

1) had been submitted to Sahlgrenska University Hospital,

2) had a final discharge diagnosis of I74.3 (Embolism and thrombosis of arteries of lower extremities) according to ICD-10,

3) had sought emergency care at one of three EDs at Sahlgrenska University Hospital

***Exclusion***

Patients were excluded if they:

1) had been wrongly diagnosed with I74.3,

2) had primarily sought emergency care at another hospital than one of the EDs at Sahlgrenska University Hospital,

3) had received the diagnosis I74.3 during an outpatient visit or other visit than an ED visit,

4) had developed ALLI in hospital while treated for other diagnoses.

***Data collection***

Data collection was performed by searching the different hospital systems with medical records. Patients were identified by using the administrative platform “Elvis” using the I74.3 diagnosis code. Elvis was also used to determine priority of patients at the ED, the time of arrival to the ED for patients not transported by EMS, time to doctor, total time at the ED as well as the date of death.

For patients transported by EMS data was gathered from an application known as AmbuLink where all major data from the EMS is recorded. In the AmbuLink data concerning symptom onset, time of phone call to dispatch center, time of outcall, time of arrival to the patient, time of departing with the patient, time of arrival to hospital, as well as vital parameters and medical priority was retrieved. Medical treatment, significant symptoms, pain level as well as whether EMS staff suspected limb ischemia or not was also retrieved from the AmbuLink.

By using the platform Melior and its applications SIE View and E-Arkiv data regarding the hospital stay, treatment and clinical reasoning regarding diagnosis and choice of treatment was gathered. Data from the ED was gathered from scanned paper journals according to the

RETTS system. The RETTS system is a triage system developed by a Swedish company, Pedicare, used by the EMS and EDs in the Västra Götaland region [29].

### *Definitions*

All data entered have been defined according to data stated in medical records. In all cases the time of symptom onset reported by the patient was used, if available. When a specified time of onset wasn't available in medical records the time of onset has been defined as 12.00 (noon) at the date of onset. Morning was defined as 08.00, noon as 12.00, afternoon as 16.00 and evening as 20.00.

Severe loss of function was defined as persistent neuropathic pain requiring pharmacological treatment and/or loss of motor function resulting in reduced walking ability. Loss of function has only been reported as "yes" if there are clear medical records of sequelae.

### *Statistical methods*

Data was assembled in worksheets using Microsoft Excel 2011. All data analysis were performed using the statistics software IBM SPSS Statistics Version 23 (SPSS, Chicago, 2015). Intergroup comparisons of categorical variables were done using Fishers Exact. The non-parametric Mann-Whitney-U test was used for continuous variables. Significance has been set to $p < 0.05$.

### *Ethics*

The study was carried out within the bound of the Helsinki declaration. The study was approved by the regional ethic review board of Gothenburg, D-nr 853-15. To ensure patient integrity all files containing social security numbers or other personal information have been password protected. Only the author and the supervisor had access to these passwords. In the worksheets each patient was allocated a serial number matching a serial number in the data files, making identification impossible without the password protected data files.

## Results

### *Enrollment*

Initially 369 patients were identified as matching the diagnosis I74.3 according to ICD-10. 92 patients where excluded due to diagnosis being registered several times and patients appearing multiple times in the database. 44 patients sought emergency care at another ED than SU before transported to SU/Sahlgrenska and where therefore excluded. 56 patients where inaccurately diagnosed with I74.3 (Embolism and thrombosis of arteries of lower extremities) in the medical records. 27 patients where excluded because they did not search emergency care or they had a non-acute debut of symptoms despite being diagnosed with ALLI. Some patients developed ALLI while being treated for other conditions in hospital; these patients were also excluded from the study. 8 patients were excluded from the study for other reasons. Such a reason may be that they where not found in the medical records. After all exclusions had been performed 108 patients remained and were finally included in the study (Fig. 2).

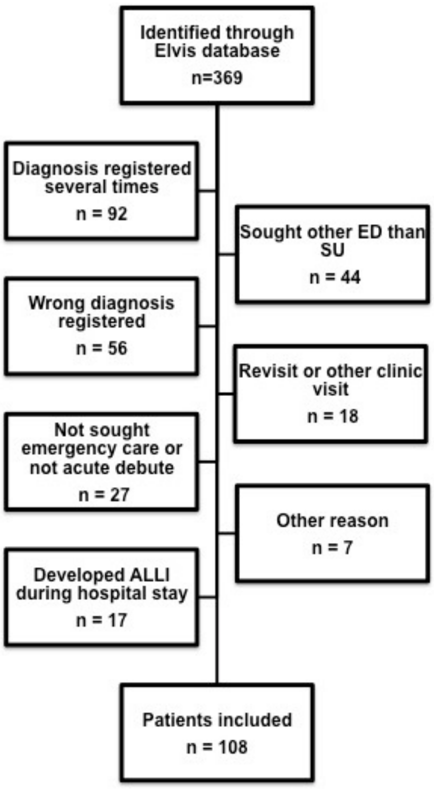


**Figure 2** – Flow chart explaining the exclusion procedure.

***Baseline data and co-morbidity***

The study thus analyzed a total of 108 patients. The patients were divided into two groups to facilitate comparison, patients transported by EMS to hospital (EMS) and patients not transported by EMS (NON) as shown below in table 1. Of the 107 patients 62 (58 %) patients were transported by EMS and 45 (42 %) used other transport. Among the studied patients was mean age 76.8 (CI 95%, 74.4 – 79.2) years and 54 (50.5 %) of patients being of male gender. Many of the patients had several co-morbidities. More than 50 % of patients included in the study suffered from hypertension, PAD or atrial flutter/fibrillation. A large proportion of patients were either current smokers (n=23, 21.6 %) or previous smokers (n=36, 35.3 %), i.e. more than half of patients (n=59, 56.9 %) had a smoking history.

In the EMS group median age was 82.5 while median age in the NON group was 74 years. When comparing the two groups (EMS versus NON) several differences in co-morbidity were noted. There were statistically significant differences in the prevalence of congestive heart failure (48.4 % vs. 13.3 %, $p<0.001$), atrial fibrillation (77.4 % vs. 35.6 %, $p<0.001$), stroke (38.4 % vs. 15.6 %, $p=0.01$), PAD (46.8 % vs. 68.9 %, $p=0.03$) and previous arterial surgery (4.8 % vs. 20 %, $p=0.026$), table 1.

**Table 1** – Chart describing patient demographics and comorbidities. Results are described for both groups; EMS transported patients and non-EMS transported patients. The percentages for the entire group are also displayed. P-values refer to comparison between EMS and non-EMS transported patients.

| | Total (n = 107) | Ambulance transported ( n = 62) | Not ambulance transported ( n = 45) | P-value |
|---|---|---|---|---|
| Median age (years) | 79 | 82.5 | 74 | |
| Mean age +/- SD (years) | 77 +/- 13 | 81 +/- 10.5 | 71.5 +/- 14 | |
| Sex (male) | 50.5 % | 43.5 % | 60 % | **0.12** |
| Previous Myocardial Infarction | 28 % | 30.6 % | 24.4 % | **0.52** |
| Angina Pectoris | 16.8 % | 14.5 % | 20 % | **0.6** |
| Heart Failure | 33.6 % | 48.4 % | 13.3 % | **< 0.001** |
| Hypertension | 52.3 % | 56.5 % | 46.7 % | **0.33** |
| Diabetes Mellitus | 17.8 % | 16.1 % | 20 % | **0.62** |
| Atrial flutter/ fibrillation | 59.8 % | 77.4 % | 35.6 % | **< 0.001** |
| Stroke | 29 % | 38.4 % | 15.6 % | **0.01** |
| Peripheral arterial disease | 56.1 % | 46.8 % | 68.9 % | **0.03** |
| Implanted stent/graft in affected vessel | 11.2 % | 4.8 % | 20 % | **0.03** |
| Malignancy | 17.8 % | 17.7 % | 17.8 % | **1.000** |
| Renal disease | 11.2 % | 16.1 % | 4.4 % | **0.07** |
| Smoker | 21.6 % | 19 % | 25 % | **0.48** |
| Previous smoker | 35.3 % | 34.5 % | 36.4 % | **1,000** |

The 30-day overall mortality was 14 %. In patients with a history of stroke the 30-day mortality was 29 % compared to 9 % for patients without previous stroke (p=0,011). The overall one-year mortality was 33 %. One-year mortality among patients with previous stroke was 52 %, compared to 25 % in the non-stroke subgroup (p=0.018). No other significant relationships between co-morbid status and ALLI outcome could be found in terms of risk of death or amputation during the subsequent 30 days and one year.

***Intervention***

Patients treated with thrombolysis (n=48) had a lower amputation rate at 30-day follow-up compared to patients treated with thrombembolectomy (n=39) (n=3 (6.3%) vs. n=5 (12.8%), p=0.003). Table 3. In a 1-year follow-up of amputation figures were similar (n=3 (6.5%) vs. n=5 (14.3%), p=0.001). All amputations were done within 30 days. Table 3. There are apparent differences regarding mortality in 30 days (n=1 (2.1%) vs. n=10 (25.6%), p=0.03), table 3. In a 1-year follow up 8.9% (n=4) of patients treated by thrombolysis had deceased, while 57.1% (n=20) of patients subject to thrombembolectomy had died (p<0.001) (Table 3).

***LMWH administration***

Concerning patients given Low Molecular Weight Heparin (LMWH) or not there are noticeable trends of differences, although not statistically significant. In all four variables analyzed during follow-up (amputation and death within 30 days and one year) there were differences regarding treatment outcomes as shown in figure 3. In total, 52.6 % of patients received LMWH in the ED. At 30-day follow-up 17.6 % of patients that did not receive LMWH in the ED had to amputate the affected limb, compared to 7.1 % of patients given LMWH (Table 2). Regarding death within 30 days 17.6 % of patients not given LMWH in the ED died in relation to 10.7 % of patients given LMWH in the acute phase (Table 2). During long-term follow-up at one-year 18.8 % of patients not administered LMWH had to amputate the ischemic limb compared to 9.4 % of patients receiving LMWH (Table 2). Among patients not receiving LMWH 40.4 % died after one year whereas 26.4 % of patients given LMWH in the ED died (Table 2).

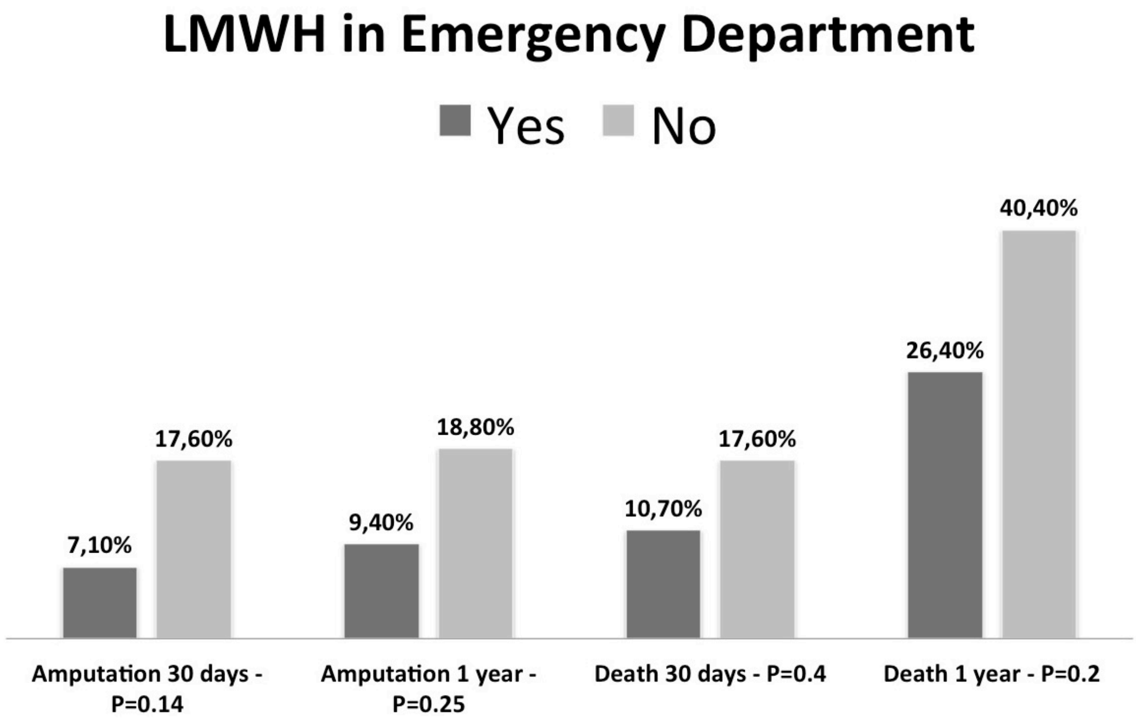


**Figure 3** – Figure displaying different outcome for patients receiving and not receiving LMWH in the ED. Percentages are also presented in table 2.

***Lead times and EMS diagnosis***

Among EMS patients, the median time from symptom onset to revascularization (surgery or thrombolysis), were 23.9 hours while the corresponding time for NON patients were 96.3 hours p=0.003.

In cases where the EMS staff suspected ALLI the time from arrival in hospital until seen by a physician was shorter than when EMS staff did not suspect ALLI (mean 81 vs. 132 minutes, p=0.009)(Table 4).

**Table 4** – Chart describing the mean and median times until patient see physician depending on whether ALLI was suspected in the ambulance.

| ALLI suspected in ambulance | Hospital arrival to physician mean (minutes) | P-value | Hospital arrival to physician median (minutes) | P-value |
|---|---|---|---|---|
| Yes | 81 | 0.009 | 52 | 0.017 |
| No | 132 | 0.009 | 102 | 0.017 |

As seen in table 5 the percentage of patients receiving LMWH in the ED is much higher among patients where ALLI is suspected in the ambulance, 52.4 % compared to 23.5 % when ALLI is not suspected (p=0.008). Among patients suspected of suffering from ALLI by the staff at the ED 56.8 % of patients received LMWH while only 9.1 % of patients not suspected of having ALLI received LMWH (p=0.003)(Table 5).

In cases (n=42) were ALLI was suspected by the EMS staff the median time from symptom onset to revascularization 17 hours compared to 55.8 hours when ALLI was not suspected, figure (p=0.011)(Figure 4).

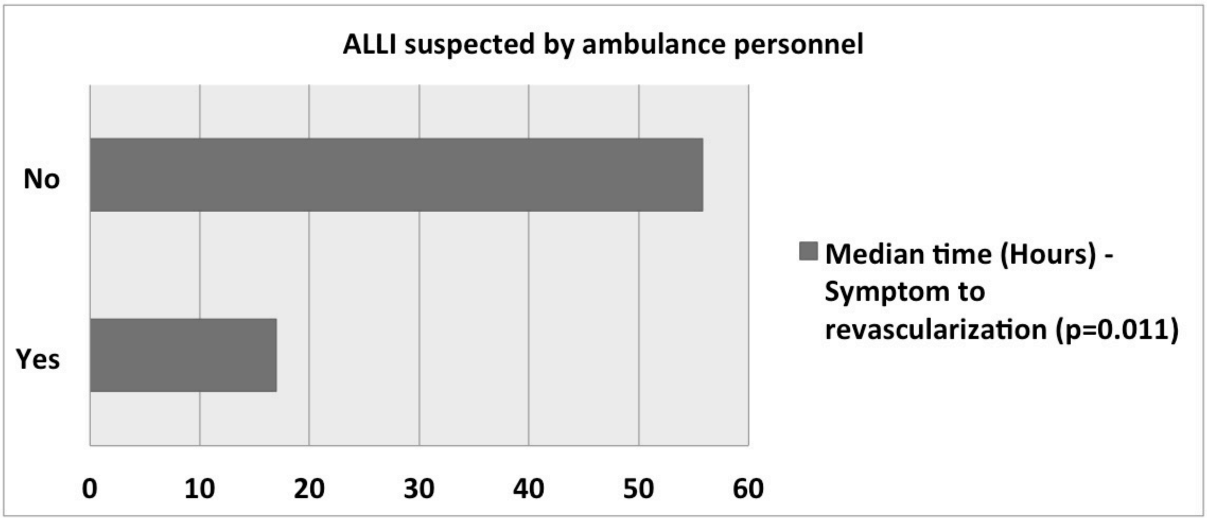


**Figure 4** – A diagram displaying the median difference in time (hours) from symptom onset to revascularization differing by whether ambulance personnel has suspected ALLI or not.

**Discussion**

The purpose of this study was to describe the early chain of care in ALLI with particular emphasis on early detection, EMS usage and early administration of LMWH. Our data suggests that an early suspicion of ALLI within the emergency health-care system is desired to achieve satisfactory treatment results. Data also tentatively suggest that early administration of LMWH might affect death and amputation outcome positively but this topic requires further research. Furthermore patients who used EMS were older and had a more severe co-morbidity than patients who did not use EMS.

Naturally there are many factors that might affect the outcome for patients with ischemia in the lower extremities. Such factors are age, co-morbidities, smoking, previous PAD and degree of limb ischemia. These factors aforementioned cannot not be regulated by the healthcare provider in the acute situation. Factors that are modifiable are the timespan to diagnosis and intervention, as well as administration of proper medications and choice of treatment modality. This study mainly examines the timespan from patient's symptom onset until several different critical points in the chain of care as well as the rate of administration of LMWH in the ED and the outcome of LMWH administration.

One factor that stood out significantly was whether EMS personnel had a suspicion of ALLI or not. In cases where ALLI was suspected in the ambulance, all lead-times were shortened resulting in more rapid diagnosis and a shorter time to revascularization. As time is an important factor all efforts that might decrease the time to revascularization are of great interest in order to provide good patient safety. Since the EMS personnel gives patients a primary priority on scene according to the RETTS-system it is very important that they are correctly educated and prepared to suspect conditions like ALLI. Since ALLI is an uncommon condition further education regarding cardinal symptoms of the disease both to EMS personnel and to the staff in the EDs is required. The ultimate objective must be that even more cases are detected before the patient is examined by a physician in the ED.

A relevant factor is that many of the more severe cases have clear-cut and typical symptoms, as mentioned above. These patients are also the ones in greatest need of emergent medical care. This might be an explanation to why certain patients receive a higher priority and are admitted to revascularization therapy earlier than patients with a less acute onset of symptoms. For patients with an Acute-On-Chronic or sub-acute onset the need for an immediate revascularization might be less urgent. Despite this, a short time to intervention is desirable among all patients to avoid chronic damage and functional loss in the affected limb.

Early administration of LMWH might have a positive effect on both amputation-rate and mortality among patients affected by ALLI. With regard to this interesting concept our study was underpowered to critically address this research question. Since the outcome varies a lot depending on several factors a high spread is likely among the groups. However, as seen in figure 3 there seems to be a signal of a more favorable outcome among patients receiving LMWH in ED. This finding is especially interesting since it may represent a very simple way to improve patient outcome. When revising current literature regarding administration of LMWH in the acute phase of ALLI no studies were found providing conclusive data regarding patient outcome. LMWH is administered in clinical praxis [1], but lacks satisfying results regarding effect in 30-day outcome [28]. More research on this topic is warranted.

In cases where patients are suspected of suffering from ALLI in either before hospital arrival or in the ED the percentages of patients administered LMWH are significantly higher indicating that these patients receive an appropriate treatment early in the chain of care compared to when ALLI is not suspected. This exemplifies how an early recognition of ALLI might directly improve treatment results.

***Limitations***

Possible limitations for this study are that the study was performed at only one medical center, and that the study only covers three years. Including other hospitals might have influenced the results, as all regional hospitals do not provide acute revascularization treatment at all times. Lack of surgical/endovascular treatment resources might lead to longer times until intervention. Including more patients, and studying a longer timespan than three years may result in a more representative picture, as the condition is not very common. A larger study population might enable more conclusive results, as multivariate analyzes in a larger population could reveal or discard correlations in a more confident manner.

A retrospective study has disadvantages compared to a prospective study. There are risks of information loss due to poor medical records, as well as that all aspects of the situation might not have been assessed correctly. A prospective study where all patients are assessed according to the SVS/ISCVS classification and randomized for LMWH treatment would likely provide a more conclusive result in this respect.

As to assess lead times the retrospective format has fewer disadvantages as times are well recorded and provide a good representation of the current chain of care. Despite this some loss of information occur due to insufficient patient records.

## Conclusion

Several conclusions may be drawn from this study. As to patient characteristics and co-morbidities it may be concluded that the groups seeking medical care for ALLI by EMS and by walk-in differ significantly. Patients using EMS are generally older and suffer from more severe co-morbidities, while walk-in patients generally have a history of previous PAD.

Of patients transported by EMS the group were ALLI was suspected had a significantly shorter time to see a physician at the emergency department compared to cases were EMS personnel did not suspect ALLI. Similar significant patterns may be recognized in time from symptom onset to revascularization therapy, as patients are admitted to revascularization faster when ALLI has been suspected since the start of the chain of care. These patients are also more likely to receive LMWH at the emergency department.

This study also suggests that an early administration of LMWH could lead to beneficial outcomes regarding amputation rate and mortality in ALLI. Further studies are needed to fully assess this relationship.

## Populärvetenskaplig sammanfattning

## Diagnos och behandling av akut nedre extremitetsischemi och dess effekt på behandlingsresultatet

Akut nedre extremitetsischemi är ett allvarligt tillstånd där artärer i benen på patienter har blockerats. De vanligaste anledningarna till detta är att en blodpropp bildas lokalt i kärlet, eller att en blodpropp lämnar hjärtat och fastnar i kärlet. Att en blodpropp lämnar hjärtat kan bero på att patienten lider av förmaksflimmer eller förmaksfladder. När en blodpropp blockerar blodkärlet stoppas blodflödet till benet, vilket leder till att vävnad dör efter en tid. I akutskedet kan patienten uppleva smärta, förlamning, blekhet, kyla och känselnedsättning i benet. Det finns två huvudsakliga metoder för att åtgärda detta, antingen genom att via en kateter inlagd i blodkärlet ge ett propplösande läkemedel eller genom att kirurgiskt avlägsna proppen.

Målet med denna studie var att undersöka vilka faktorer som kan påverka handläggningstiden och därmed behandlingsresultatet, från det att patienten insjuknar i extremitetsischemi till dess att kärlet åter blir öppnat och benet återfår blodförsörjning. Målet var också att kontrollera huruvida administration av det proppförebyggande läkemedlet Lågmolekylärt Heparin (LMWH) påverkar utfallet för patienterna. 108 patienter analyserades genom att följa upp journaler från Sahlgrenska Universitetssjukhuset.

Vad man såg var att patientgruppen som sökte vård med ambulans skilde sig från gruppen som tog sig till akutmottagningen på egen hand. De som blev ambulanstransporterade var generellt äldre och hade andra grundsjukdomar än gruppen som tog sig till akutmottagning på egen hand. Av de som tog sig till akutmottagning på egen hand hade fler patienter tidigare problem med dålig blodförsörjning i benen. Man såg också att av de patienter som transporterades med ambulans så skiljde sig handläggningen markant beroende på huruvida ambulanspersonalen misstänkte akut nedre extremitetsischemi eller ej. Om ambulanspersonalen misstänkte extremitetsischemi var tiden tills patient fick träffa läkare lägre än om tillståndet ej misstänkes. Detsamma gäller tiden till att blodflödet kunde återställas i patientens ben.

För patienter som fick LMWH på akutmottagningen noterades en trend att risken för amputation och död minskade gentemot de patienter som inte fick LMWH.

Det kan således konstateras att en tidig klinisk misstanke och tidig korrekt diagnostik minskar tiden till kärlintervention avsevärt. Att ytterligare utbilda personal i ambulans och på akutmottagningar avseende detta kan sannolikt minska handläggningstiden för fler patienter och leda till korrekt utredning och en tidigare behandling.

Avseende administration av LMWH är resultatet ej konklusivt och en större studie bör göras på området för att lättare kunna påvisa signifikanta samband. Resultatet pekar dock i en riktning som talar för en gynnsam effekt av läkemedlet i akutläget.

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## Tables, Figures and Appendices

**Table 2** – Table displaying the rate of amputation and mortality within 30 days and 1 year depending on whether Low Molecular Weight Heparin (LMWH) was administered or not.

| LMWH | Amputation 30 days – p= 0.14 | Amputation 1 year – p= 0.25 | Mortality 30 days – p= 0.4 | Mortality 1 year – p= 0.2 |
|---|---|---|---|---|
| Yes | 7.1 % | 9.4 % | 10.7 % | 26.4 % |
| No | 17.6 % | 18.8 % | 17.6 % | 40.4 % |

**Table 3** – Table displaying the rate of amputation and mortality within 30 days and 1 year depending on choice of intervention.

| Treatment | Amputation 30 days – p= 0.003 | Amputation 1 year – p>0.001 | Mortality 30 days – p=0.01 | Mortality 1 year – p>0.001 |
|---|---|---|---|---|
| Thrombolysis | 6.3 % | 6.5 % | 2.1 % | 8.9 % |
| Thrombembolectomy | 12.8 % | 14.6 % | 25.6 % | 57.1 % |

**Table 5** – Table describing differences in whether patients are administered Low Molecular Weight Heparin (LMWH) in relations to ALLI suspicion among ambulance personnel and ALLI suspicion in the ED.

| Treatment | LMWH in ED | P-value |
|---|---|---|
| ALLI suspected in ambulance | 52.4 % | 0.08 |
| ALLI not suspected in ambulance | 23.5 % | |
| ALLI suspected in ED | 56.8 % | 0.003 |
| ALLI not suspected in ED | 9.1 % | |