The Role of the Angiosome Concept in the Treatment of Below the Knee Critical Limb Ischemia

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ACADEMIC DISSERTATION

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Helsinki 2017
To my beloved family…
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This thesis is based on the following publications:


III. Špillarová K; Settembre N; Biancari F; Albäck A; and Venermo M., Angiosome-targeted PTA is more important in endovascular revascularization than in surgical revascularization: Analysis of 545 patients with ischaemic tissue lesions. Eur J Vasc Endovasc Surg 2017 Feb 16. pii: S1078-5884(17)30055-2


In the text, the publications are referred to by their Roman numerals.
ABBREVIATIONS

ABI – Ankle brachial index
ADP – Arteria dorsalis pedis
AFS – Amputation-free survival
AP – Arteria peronealis
ASP – Ankle systolic pressure
ATA – Arteria tibialis anterior
ATP – Arteria tibialis posterior
BASIL - bypass versus angioplasty in severe ischemia of the leg
CAD – Coronary artery disease
CKD – Chronic kidney disease
CLI – Critical limb ischemia
CRP – C-reactive protein
CV – Cardiovascular
CVD – Cerebrovascular disease
DFU – Diabetic foot ulcer
DM – Diabetes mellitus
DR – Direct revascularization
DSA – Digital subtraction angiography
EVT – Endovascular therapy
HUCH – Helsinki University Central Hospital
IBS – Infrainguinal bypass surgery
IC – Intermittent claudication
MRA – Magnetic resonance angiography
PAD – Peripheral arterial disease
PTA – Percutaneous transluminal angioplasty
PVR – Pulse volume recording
SVS/ISCVS – Society for Vascular Surgery/International Society for Cardiovascular Surgery

TASC – Trans-Atlantic Inter-Society Concensus Document on Management of Peripheral Arterial Disease

TcPO2 – Transcutaneous partial oxygen pressure

TP – Toe pressure

WHO – World Health Organization
ABSTRACT

**Background:** Critical limb ischemia (CLI) presented as a foot ulcer with or without gangrene requires the quick re-establishment of arterial blood supply. The recently introduced angiosome concept has offered a new perspective on the treatment of CLI. The idea of angiosome-targeted (direct) revascularization—the restoration of blood flow directly to the angiosome affected by an ischemic wound—appeared among vascular surgeons.

The concept has risen interest among vascular specialists as several studies supported the hypothesis of a better clinical outcome after direct revascularization. Despite the promising results, the feasibility of the concept in endovascular treatment has not been addressed, nor has a comparison of revascularization methods, endovascular versus open surgical, been investigated. Furthermore, the methodology is not consistent, and the definition of direct revascularization is unclear, especially if the wound spreads over several angiosomes. Therefore, clinical value of the hypothesis is yet to determined.

**Aim of the study:** The aim of this study was to investigate the importance of the angiosome concept in the treatment of CLI with tissue loss (Rutherford 5,6). The main goals were to evaluate the feasibility of the concept in endovascular procedures; to compare the clinical outcomes of direct and indirect revascularization; and to obtain a consensus concerning the angiosome-targeted approach.

**Patients and methods:** The study comprises patients referred for infrapopliteal revascularization, endovascular or open surgical, between 2008 and 2013. We analyzed patient’s records retrospectively, focusing on wound location, the feasibility of infrapopliteal direct revascularization, and differences in clinical outcome, with the main interest in wound healing and leg salvage. We also compared the clinical outcome of two existing definitions of angiosome-targeted revascularizations as they differ in revascularization approach of lesions located in forefoot and the heel. Definition A accepts into the direct group if any of the affected angiosomes is revascularized, while Definition B accepts only revascularization of posterior tibial artery.

**Main Results:** For the feasibility of the angiosome concept in endovascular infrapopliteal revascularization, the wound was isolated to a single angiosome in only 24% of the cases, and 33% of the patients had only one infrapopliteal artery suitable for revascularization. The success rate of direct revascularization, however, was 75.9%.

When comparing direct and indirect revascularization, the propensity score analysis yielded significantly better leg salvage ($p=0.019$) and a trend towards improved wound healing ($p=0.058$) for the direct approach, and when adjusted for revascularization method, direct bypass was associated with a significantly higher wound-healing rate than endovascular revascularization (HR 1.295, 95%CI 1.005–1.668).

Among diabetic patients, the findings showed that direct bypass yielded significantly better wound healing than indirect PTA ($p=0.001$, HR 2.83, 95%CI 1.35–3.04), and, furthermore, indirect PTA was associated with the poorest leg salvage rate.
The analysis of the two different angiosome-targeted approaches revealed a significantly better feasibility of the conventional method (definition A) compared to definition B (p<0.05). Furthermore, the prognostic ability for better clinical outcome using definition A was confirmed by both the Cox proportional hazard analysis (p= 0.044 for wound healing, p= 0.047 for leg salvage) and the propensity score analysis (p= 0.037 for wound healing, p= 0.044 for leg salvage).

**Conclusion:** The tissue lesion affects several angiosomes in the majority of the cases, and a consensus on the accurate definition of angiosome-targeted revascularization needs to be achieved to standardize the methodology of arterial selection. Despite the inconsistent methodology in the literature, our findings seem to suggest that observing the angiosome concept in the decision-making yields better clinical outcomes, especially in endovascular therapy. In bypass surgery, however, the concept seems to be of less value, and the artery with the best runoff should be selected as the outflow artery.
INTRODUCTION

Critical limb ischemia (CLI) presented as a foot ulcer with or without gangrene is a serious impairment of a patient’s health status and requires a quick re-establishment of arterial blood supply. The incidence of CLI is expected to rise with the increasing proportion of the elderly population as well as prevalence of diabetes mellitus (DM) (Rothwell et al. 2005, WHO, Armstrong et al. 2013), which are significant risk factors for the progression of asymptomatic peripheral artery disease or claudication into CLI (Norgren et al. 2007, Thiruvoipati et al. 2015).

The direction of treatment, in terms of revascularization options, has changed dramatically, shifting towards an “endovascular first” strategy and decreasing the number of patients primarily referred for open surgical revascularization (Goodney et al. 2009). Irrespective of the revascularization method, the literature states that pulsatile flow to the correct region of the foot is necessary to heal ischemic tissue loss (Treiman et al. 2003, Hughes et al. 2004). Defining such a region for revascularization, however, remains under debate.

The recently introduced angiosome concept has offered a new perspective on revascularization location. An angiosome was defined by Taylor et al. (1987) as a three-dimensional block of tissue supplied and drained by specific, “angiosomal vessels.” In 2006, Attinger et al. presented that the foot consist of 6 angiosome regions, each supplied by one of the crural arteries and its terminal branches. The concept of angiosome-targeted (direct) revascularization is based on this division, and direct revascularization (DR) refers to the selective revascularization of the specific artery feeding the angiosome that is affected by an ischemic ulcer (Varela et al. 2010, Söderström et al. 2013, Neville et al. 2009, Azuma et al. 2012, Acín et al. 2014, Kret et al. 2014).

Two meta-analyses, including a total of 15 studies, have reported better clinical outcomes in favor of direct revascularization, especially in patients with diabetes (Bosanquet et al. 2014, Biancari and Juvonen 2014). However, the feasibility of the concept has not been investigated, nor has there been a comparison between revascularization methods—endovascular treatment versus open surgical. Furthermore, the methodology of DR is not consistent in the literature, and two different definitions of DR exist (Varela et al. 2010, Söderström et al. 2013, Alexandrescu et al. 2013). Therefore, we focused our interest on these issues in the present study.
**REVIEW OF THE LITERATURE**

**Peripheral arterial disease**

1.1.1 Definition
Peripheral arterial disease (PAD) is defined as a narrowing the lumen of peripheral arteries, with the exception of those supplying the brain and heart. The narrowing is caused by diffuse atherosclerosis—a systemic inflammatory disease leading to the development of an atherosclerotic plaque.

The pathophysiology of atherosclerosis has been studied intensively over the past decade. It seems to be a degenerative inflammatory process of the vessel wall, starting with endothelial dysfunction and leading to an increased permeability to lipoproteins and other plasma constituents. This causes the migration of leucocytes and monocytes-macrophages into the subendothelial space. The production of inflammatory mediators stimulates the proliferation of smooth muscles in the intima, forming a fibrous cap that weakens the mechanical stability of the plaque and separates the lipid-rich thrombogenic core from the lumen and circulating blood (Mitchell and Sidawy 2005).

PAD can be determined with a simple non-invasive procedure by calculating the ankle-brachial index (ABI), which has high sensitivity and specificity. An ABI value between 1–1.4 is considered normal, while 0.9 or less indicates PAD. ABI values of 0.91–0.99 are considered borderline and values >1.4 indicate non-compressible arteries (Rooke et al. 2011).

1.1.2 Epidemiology
The prevalence of PAD rises sharply with age—while PAD affects 12–14% of the general population, the figure rises to 20% at the age of ≥75 years (Crigui and Aboyans. 2015). The incidence of PAD in the male population is 1.7/1000 at the age of 40–54 years, 1.5/1000 at the age of 55–64 years, and 17.8/1000 at the age of over 65 years. The annual incidence among women increases after menopause: 22.9/1000 at the age over 65 years (Hooi et al. 2001). Even though the male population has lower incidence rates, both the incidence and prevalence of symptoms in terms of intermittent claudication (IC) are twice as high among men compared to a women (Kannel and McGee. 1985, Meijer et al. 1998, and Murabito et al. 2002).

A study by Allison et al. (2007) performed on a large American population showed that the prevalence also varies dramatically between ethnic groups. While approximately 20% of the non-Hispanic white population suffered from PAD at the age of 80 years, the rate for African Americans was twice as high.

Globally, within one decade (2000-2010) the number of individuals with PAD increased by 28.7% in low-income and middle-income countries and by 13.1% in high-income countries (Fowkes et al. 2010). The prevalence is likely to increase even further in the future due to the growing number of older people with a prolonged life expectancy (WHO).
1.1.3 Risk factors
Unlike the risk factors of coronary artery (CAD) and cerebrovascular disease (CVD), which have been studied extensively (Donnelly and Yeung 2002), the amount of literature focusing only on PAD risk factors is limited. The reason is that the onset of PAD as defined by the ABI is asymptomatic in two thirds of patients and, therefore, it is unlikely to be documented in the records of healthcare providers (Sigvant et al. 2007, McDermott et al 2000). However, five large epidemiological studies, similar in materials and methods, allow a reasonable comparison of the most common risk factors (Murabito et al. 2002 and 1997, Newman et al. 1993, Meijer et al. 2000, and Allison et al. 2007).

1.1.3.1 Smoking
There is a significant, independent association between PAD and smoking. The association is even stronger than between smoking and CAD (Dormandy and Rutherford. 2000). Current smoking increases the probability of developing PAD 2–4-fold. A clear dose-response relationship between smoking and the risk of PAD was observed (Fowkes et al. 1992, Willigendael et al. 2004). Even the age at the onset of smoking showed a significant increase in risk when a person started smoking at an age of ≤16 years (Planas et al. 2002).

Current smoking is the most important modifiable risk factor for symptomatic PAD and the development of critical limb ischemia, as smoking promotes endothelial dysfunction and alters lipid metabolism and coagulation (Lu and Creager 2004). Furthermore, smokers have a higher risk of peri- and postoperative complications in connection with both percutaneous interventions and open surgery (Shammas et al. 2007), which leads to an increased risk of amputation and mortality (Lassila and Lepäntalo. 1988, Galaria et al. 2005). Even though the risk of PAD stays elevated even 20 years after smoking cessation (Joosten et al. 2012), quitting smoking slows down the progression of PAD and relieves the symptoms (Collison and Donelly 2006). Therefore, all patients should be informed of the consequences and encouraged to stop smoking.

1.1.3.2 Diabetes mellitus
Diabetes is one of the strong predictors of PAD and plays the main role in the progression of the disease, making these patients more prone to ischemic events with impaired functional status when compared to patients without diabetes (Thiruvoipati et al. 2015). Glucose intolerance is associated with a 20%–30% prevalence of abnormal ABI as opposed to the 7% in those with normal glucose tolerance (Beckman et al. 2002). The severity and duration of diabetes are predictors of both the incidence and extent of PAD, as each 1% increase in glycosylated hemoglobin (HbA1C) correlates with a 28% increase in incidence of the disease (Selvin et al. 2006, Jude et al. 2001).

In patients with diabetes the PAD affects mainly the infrapopliteal arteries, in addition diabetic patients experience a later onset of symptoms due to concomitant peripheral neuropathy (American Diabetes Association 2003). Nerve malfunction diminishes sensory feedback and minimizes pain perception. This leads to late reporting to the clinician; the
disease is usually already advanced, such as an ischemic ulcer or gangrene (Hirsch et al. 2006, Setacci et al. 2009, Jude et al. 2001).

Diabetic patients who develop critical limb ischemia, 30% will undergo major amputation, and the 6-month mortality rate among them is 20% (Dormandy and Rutherford. 2000). The increased severity of PAD may be explained by a different pathophysiology of atherosclerosis, as diabetes is multifactorial and includes inflammatory processes (Pradhan et al. 2001, Paneni et al. 2013 and Beckaman et al. 2013), derangements of various cell types within the vascular wall (Troidl and Schaper 2012, Suzuki 2001, Uemura 2001), the promotion of coagulation (Armstrong et al. 2013, Carr 2001), and the inhibition of fibrinolysis (Vinik et al. 2001). Such factors lead to higher susceptibility of the vessel to atherosclerosis as well as the instability of the plaque (Thiruvoipati et al. 2015).

Globally, over 170 million people suffer from DM, and the number is projected to increase to 366 million by 2030 (Armstrong et al. 2014, Wild et al. 2004). Therefore, early administration of treatment, good follow-up and collaboration between different specialists are needed to improve the clinical outcome.

1.1.3.3 Dyslipidemia
The role of dyslipidemia in PAD is still not as clear as the role of smoking and diabetes mellitus (Reiner et al. 2011). Total cholesterol has been examined as a potential risk factor in several studies, and it was significantly associated with PAD in multivariable analysis in the majority of the studies (Newman et al. 1993, Bainton et al. 1994, Meijer 2000).

Only one study reported a significant association between dyslipidemia and PAD when using univariate analysis (Murabito et al. 2002). On one hand, the Framingham study showed that a fasting total cholesterol level greater than 7 mmol/L was associated with twice as high an incidence of the progression from asymptomatic to symptomatic PAD (Kannel 1994). On the other hand, a study by Mowat et al. (1997) comparing patients with PAD to healthy controls suggested that the protective role of high-density lipoprotein (HDL) might play a more important role than the atherogenic effect of low-density lipoprotein (LDL). A few studies also found an association between an increased level of triglycerides and PAD. This may be due to the fact that abnormal levels of triglycerides are often present in DM and metabolic syndrome, which themselves are risk factors for PAD and its progression (Smith et al. 1996, Stalenhoef and de Graaf 2008).

Treatment with statins reduces the incidence of PAD progression (Pedersen et al. 1998, Hearth Protection study Collaborative group 2002), as it not only has a lipid-lowering effect, but also an anti-inflammatory effect and the ability to modulate thrombogenesis providing plaque stabilization (Rice and Lumsden 2006, Hou et al. 2015). However, the recent guidelines of the American College of Cardiology/American Heart Association (Stone et al. 2014, Robinson and Stone 2015) recommend statin therapy in high-risk CAD patients with a greater burden of atherosclerosis and avoiding the treatment in patients with lower risk and little atherosclerosis.
1.1.3.4 Hypertension and blood pressure

There is evidence that hypertension is a strong risk factor for all forms of CVD; however, the association with PAD is not fully understood (Rahimi et al. 2015). The study by Emdin et al. (2015), studying the impact of blood pressure on PAD, showed that systolic pressure (SP) is a significant risk factor, as a SP of 20mmHg higher than usual resulted in a 63% higher risk of PAD and a 10mmHg higher diastolic blood pressure was associated with a 35% increase. The severity of the PAD paralleled with the severity of hypertension in the Edinburg Artery Study (Fowkes et al. 1992), but a later study concluded that hypertension is not significantly associated with the progression of PAD to CLI which puts the impact of hypertension into question (Wyss et al. 2015).

Hypertension and atherosclerosis may be regarded as two effects with one underlying cause. Hypertension affects the atherosclerosis by mechanical stress changing the endothelial and other cell functions, and atherosclerosis affects hypertension by reduced arterial compliance and increased peripheral resistance (Takahashi et al. 1993). A good management of hypertension is of great value as the blood pressure potentiates with other risk factors, leading to a greater risk of cardiovascular disease events (Mancia et al. 2013).

1.1.3.5 Age

Age is the most important non-modifiable risk factor, as mentioned earlier both the prevalence and incidence of PAD rise sharply with aging (Crigui and Aboyans. 2015). Aging also plays an important role in the occurrence of symptoms (Intermittent claudication), as the prevalence increases from approximately 3% at the age of 40 years to 6% at the age of 60 (Norgren et al. 2007).

1.1.3.6 Ethnicity

After age, the ethnicity is the second most important non-modifiable risk factor. Although data on the association of ethnicity with PAD are limited, several recent studies have suggested a higher risk among the black population (Guerchet et al. 2012, Zheng et al. 1997, Criqui et al. 2005, Allison et al. 2006). The higher prevalence of PAD among African Americans has been confirmed in the GENOA (Genetic Epidemiology Network of Arteriopathy) study—34% for women and 33% for men. The GENOA study also showed that the difference in PAD prevalence was associated with different conventional risk factors (Kullo et al. 2003).

1.1.3.7 Others

1.1.3.7.1 Chronic kidney disease

There is an association between renal insufficiency and PAD, especially in the case of end-stage renal disease requiring dialysis (O’Hare and Johansen. 2001, Joosten et al. 2014). Furthermore, in case of concomitant chronic kidney disease, the poorer outcomes have been reported in terms of both leg salvage and mortality (Lacroix et al. 2013).
1.1.3.7.2 C-reactive protein (CRP) and fibrinogen
A recent study showed that the risk of developing PAD is significant and independent, with odd ratios of the upper versus lower quartiles of 2.8 for CRP and 2.2 for fibrinogen (Ridker et al. 2001).

1.1.3.7.3 Homocystein
The association of homocystein with PAD has been studied widely, and the findings differ dramatically. While a meta-analysis published in 1995 suggested an odds ratio of 6.8 for a 5micromol/L difference in fasting total homocystein (Boushey et al. 1995), a more recent large European case-control study estimated an odds ratio of 1.7 (Graham et al. 1997). The suggestion that hyperhomocysteinemia is an independent risk factors has been sustained.

1.1.4 Classification
Generally, disease progression results in the appearance of symptoms—the more severe the disease the sicker the patient, leading him/her to seek medical attention. An early onset of symptoms results in quicker examination and treatment, which may improve the clinical outcome. However, in patients with PAD, the severity of the disease is not parallel to the development of symptoms in all cases, as the main factors driving the appearance of symptoms are 1) the patient’s activity level and 2) the number of comorbidities, such as congestive heart failure, musculoskeletal disease or diabetes, that can prevent the person from experiencing warning symptoms (claudication, leg pain) (Norgren et al. 2007).

1.1.4.1 Asymptomatic
The clinician should suspect PAD in the context of missing or compromised pulses during an examination of the lower limb. Lower values of ABI measurements confirm the diagnosis—the reduction may vary from mild, i.e. 0.7–0.9, or moderate, 0.5–0.7, to severe, <0.5 (Shammas et al. 2007). Therefore, asymptomatic patients with a low ABI may develop critical limb ischemia, mainly due to the occurrence of non-healing wounds caused by relatively minor trauma (Norgren et al. 2007). This can lead to significant functional limitations in daily activities and most severely increase the risk of limb loss.

The cumulative incidence of deteriorating from asymptomatic to intermittent claudication (IC) over 5 years is 7% (4%–11%) and the cumulative incidence of all-cause mortality and CV events over 5 years is 19% (17%–20%) (Sigvant et al. 2016). The effectiveness of screening for PAD in asymptomatic and undiagnosed individuals in terms of a reduction in all-cause morbidity and mortality has not been determined due to the lack of randomized controlled trials (Andras and Ferket 2014).

1.1.4.2 Intermittent claudication
Claudication is defined as muscle discomfort (pain, cramps, or sense of fatigue) in the lower limbs (calf, thigh, or buttocks) related to exertion that relieves by a few minutes of
rest (Walker et al. 1990). The symptoms originate from an occlusive lesion that does not limit the blood flow at rest but, with exercise, causes a significant decrease in muscle perfusion, leading to a mismatch between oxygen supply and the muscle’s metabolic demand (Norgren et al. 2007).

Approximately 10%–35% of patients with PAD will present with classic IC. The underlying cause of the arterial occlusion, however, should be confirmed by ABI measurement as symptoms with normal values most likely have a different non-vascular origin (e.g., nerve root compression, spinal stenosis, arthritis) (Hirsch et al. 2006). The cumulative incidence rate of progressing to critical limb ischemia is 46.6 (26.0–67.7), corresponding to 21% (12%–29%) over 5 years, and the incidence of all-cause mortality and CV events over 5 years is nearly doubled compared to asymptomatic patients (Sigvant et al. 2016).

Today, the therapeutic management consist more of conservative treatment (supervised exercise programs, altering modifiable risk factors, antiplatelet therapy) rather than invasive interventions (Kobayashi et al. 2015). Regular exercise initiates the growth of collateral vessels, and 50% of patients become symptom-free over a 5-year follow-up (Dormandy et al. 1999). The amputation rate in claudicants according to the TASC document is relatively low, 1%–3% (Norgren et al. 2007), but a more recent review found a higher rate of amputations, ranging between 4%–27% (Sigvant et al. 2016).

1.1.4.3 Critical limb ischemia (CLI)
The problems of CLI are discussed in a separate section; please see section 2.2.

1.1.4.4 Acute limb ischemia (ALI)
Acute limb ischemia usually presents with a rapid development of rest pain in the limb and a loss of pulses. In PAD, the vessel is typically occluded by a thrombus that has formed on top of the atherosclerotic lesion. Another cause may be embolization from higher up in the vascular tree. Due to minimal or non-existing collaterals, the viability of leg is highly threatened and requires emergency treatment (Shammas et al. 2007, Norgren et al. 2007).

1.1.5 Atherosclerotic disease in other vascular territories
Atherosclerosis causes not only PAD but also CAD and CVD, and they therefore often occur together. The PARTNERS study showed that nearly one in three patients with PAD suffered from either symptomatic or asymptomatic CAD (Hirsch et al. 2001). The rate of co-existing symptomatic CVD seems to be lower compared to CAD, as only roughly 5% will have a history of any cerebrovascular event. Despite the low incidence of cerebrovascular symptoms, CVD occurs upon ultrasonography in 26%–50% of all claudicants (Norgren et al. 2007). There is considerable overlap between the vascular territories (Figure 1; Bhatt et al. 2006), which poses particular challenges in terms of diagnosis and treatment.
Figure 1. The overlap between the vascular territories in patients with multivascular disease, calculated from the REACH study (modified from Bhatt et al. 2006).
Critical limb ischemia (CLI)
Critical limb ischemia is the most severe stage of PAD, represented by rest pain in the lower extremity or tissue loss with or without gangrene (dry or humid). Its treatment is a major burden on health care resources, with poor survival (Barshes et al. 2011).

1.1.6 Definition
The definition of CLI has evolved over time (Table 1) and still lacks complete consensus. The first classification to be introduced, based on clinical symptoms (Fontaine et al. 1954), is still in use by some clinicians. A more precise and the latest definition was introduced by the Trans-Atlantic Inter-Society Consensus Working Group (TASC) which suggests always suspecting CLI in patients who present with foot rest pain lasting more than two weeks, or a foot lesion (dry or humid gangrene) (Norgren et al. 2007). Lower values of leg perfusion measurements confirm the diagnosis of CLI—these include ankle brachial index, toe pressure, ankle pressure, or transcutaneous oxygen perfusion (Table 1). The lack of consensus on the CLI definition may lead to bias when studying the CLI population.
<table>
<thead>
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<th>Year</th>
<th>Definition</th>
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| 1954 | **Fontaine Classification (Fontaine et al.)**  
- *Stage III*: Rest pain caused by arterial insufficiency  
- *Stage IV*: Ulcer and/or gangrene (dry or humid) caused by arterial insufficiency |
| 1982 | **International Vascular Symposium Working Party Definition (Bell et al.)**  
- Severe rest pain requiring repeated analgesia for at least 4 weeks and ankle pressure <40mmHg  
- In the presence of tissue necrosis or digital gangrene, ankle systolic pressure (ASP)<50mmHg (diabetics should be defined as a separate group) |
| 1989 | **European Consensus Document on Critical Limb Ischemia**  
- Severe rest pain requiring analgesia for at least 2 weeks and ASP <50mmHg |
| 1992 | **Second European Consensus Document**  
- Persistently recurring ischemic rest pain requiring analgesia for at least 2 weeks or tissue loss (ulceration or gangrene), and ASP <50mmHg and/or toe pressure (TP) <30mm |
| 1997 | **Rutherford Classification (Rutherford et al.)**  
- *Grade II, category 4*: Ischemic rest pain and resting ASP<40mmHg, flat or barely pulsatile ankle/metatarsal pulse volume recording (PVR), or TP<30mmHg  
- *Grade III, category 5*: minor tissue loss and resting ASP<60mmHg, flat or barely pulsatile ankle/metatarsal pulse volume recording (PVR), or TP<40mmHg  
- *Grade IV, category 6*: major tissue loss extending above the metatarsal level, functional foot not salvageable, and resting ASP<60mmHg, flat or barely pulsatile ankle/metatarsal pulse volume recording (PVR), or TP<40mmHg |
| 2000 | **Trans-Atlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC Working Group) (Dormandy et al.)**  
- Clinical definition: chronic, ischemic rest pain, ulcers or gangrene attributable to objectively proven arterial occlusive disease  
- Definition for trials: ASP<50–70mmHg or TP<30–50mmHg or TcPO2 <30–50mmHg |
| 2007 | **Trans-Atlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) (Norgren et al.)**  
- Chronic ischemic rest pain, and ASP<50mmHg or TP<30mmHg  
- Ulcer or gangrene, and ASP<70mmHg or TP<50mmHg |
1.1.7 Epidemiology
Despite the excessive research on CLI, not much is known about the epidemiology. A recent meta-analysis estimated a pool prevalence of 800 cases per an adult population of 100,000 (Biancari et al. 2013). However, the incidence differs within the literature. The only prospective population-based study, the Oxford Vascular Study, has estimated an incidence of 22/100,000 per year with a sharp increase among the elderly: 67 cases in the age group of 65–74 years, 168 cases in the age group of 75–84 years, and 171 cases in the age group of ≥85 years (Rothwell et al. 2005). On the other hand, the study by Baser et al. (2013), evaluating the US Medicare population aged ≥65 years, reported an incidence of 200/100,000 per year. A continuing increase in the incidence is expected as the proportion of the elderly population is on rise (WHO).

1.1.8 Natural history
The different approaches to how to treat CLI as well as the varying skills of the clinicians in each vascular center makes it very difficult to study the natural history of critical limb ischemia objectively (Luther et al. 2000, Bradbury et al. 2002, Paulus et al. 2012). The direction of treatment, in terms of revascularization options, has changed dramatically. In the late 20th century (1980–1999), only 50% of the patients underwent some form of revascularization; approximately 25% received conservative treatment and 25% underwent a primary amputation (Dormandy et al. 1999). During the last decade, up to 90% of patients with CLI have had an attempt of revascularization, especially in active interventional centers (Norgren et al. 2007). A recent retrospective study reviewing 1244 patients who underwent endovascular treatment reports different one-year overall survival and freedom from major amputation rates between patients with rest pain and tissue loss; 87% and 94% versus 80% and 81%, respectively (Vierthaler et al. 2015). The only randomized controlled trial comparing open surgical bypass to endovascular treatment, the BASIL (bypass versus angioplasty in severe ischemia of the leg), reported similar overall survival and amputation-free survival in both groups at 2 years’ follow-up, but after 2 years, the clinical outcomes were better in the open surgery group (Bradbury et al. 2010).

The least biased data on the natural history of the CLI is provided with a group of patients that are not suitable for active treatment (endovascular/surgical). Two meta-analyses including a total of 13 studies reported similar results: an all-cause mortality rate in one-year follow up of 22% and a one-year pooled leg salvage rate of 57.4% (Abu Dabrh et al. 2015, Biancari et al. 2013). Indeed, the mortality and number of major amputations are high among patients with untreated CLI, but there is evidence of improvement over time. In 1995, Jivegård et al. reported a leg salvage rate of 45% and an amputation-free survival rate of 33% over 18 months. One year later, Lepåntalo and Mätzke (1996) studied the outcome of 105 patients with 136 critically ischemic legs treated conservatively. At one-year follow-up, the all-cause mortality was 54% and the amputation rate 46%.

The exact reason for improvement is unclear, but it is likely related to a prompter diagnosis of CLI, improvements in the medical treatment of comorbidities as well as local wound care and new therapy techniques (Teraa et al. 2013).
1.1.9 Diagnosis

The diagnosis of critical limb ischemia is based on clinical findings: the patient’s anamnesis and physical examination. The majority of the patients do not experience the early symptoms—therefore, when examining any patient with leg pain or a foot ulcer, a vascular cause should be considered. The foot of a critically ischemic leg is usually pale, cold, cyanotic, and without pedal pulses. The tissue loss frequently develops distally to the ankle region, and, if not infected, it may form dry gangrene (dry, shrunken and dark reddish-black eschar) and become mummified. The objective investigations of arterial flow confirm the CLI diagnosis. The available measurement methods with values indicating CLI are listed below:

1. Ankle pressure (AP): An easy method feasible in primary care centers. Values of < 50mmHg in chronic ischemic rest pain and <70mmHg in patients with ulcer or gangrene indicate CLI.

2. Toe pressure (TP): Measurement performed in vascular laboratories. Values are typically <30mmHg in chronic ischemic rest pain and <50mmHg in patients with an ulcer, gangrene, or diabetes.

3. Transcutaneous oxygen tension (TcpO2): Measurement performed in vascular laboratories. The critical level is <30mmHg.

4. Investigation of microcirculation: These measurements are mainly used as research methods. Capillaroscopy (Kluz et al. 2013), indocyanine green angiography (Terasaki et al. 2013), laser Doppler fluxometry (Ticcinelli et al. 2014).

If revascularization is likely to be indicated, the imaging of the lower limb arteries is mandatory. The current options are: color-assisted duplex ultrasonography, digital subtraction angiography (DSA), computed tomography angiography (CTA), and magnetic resonance angiography (MRA). DSA remains the gold standard; however, the drawbacks are its invasiveness and high radiation exposure. The evolution of CTA and MRA technologies has resulted in high accuracy in the assessment of hemodynamically significant stenosis and occlusion, as well as non-invasiveness with lower or no radiation exposure (Met et al 2009, Collins et al. 2007). The low radiation exposure is especially important among diabetic patients who are more likely to suffer from chronic kidney disease. In case of renal failure or necessity of large volumes of contrast medium for complex endovascular procedure, the carbon dioxide angiography is preferred (Cho 2015). Therefore, the imaging strategy of DSA as the gold standard is likely to change in the near future (Meyersohn et al. 2015).
1.1.10 Treatment

Patients with leg rest pain with or without foot ulcer/gangrene should be evaluated without delay. If CLI is suspected the patients should urgently be referred to a vascular surgical unit (Dormandy and Rutherford 2000, Lepäntalo et al. 2000).

The primary goal of the treatment is to restore the blood flow into the ischemic leg, which relieves pain and allows the healing of the ischemic tissue. The importance of restored pedal pulsation with foot reperfusion was already emphasized during the last century when it was mainly achieved by means of open surgical techniques (Pomposelli et al. 1990, Faglia et al. 1998).

Over the last decade, the developments in the endovascular technique have rapidly increased the number of these procedures among patients with CLI. This evolution has shifted the treatment of CLI towards an “endovascular first” strategy beyond the recommendations of TASC II (Table 2), and the number of patients primarily referred for open surgical revascularization has decreased significantly (Goodney et al. 2009). This shift in the TASC II guidance has not been emphasized enough, and, furthermore, the infrapopliteal TASC classification was missing. Therefore, an update of the consensus on revascularization strategies for PAD was discussed in a multispecialty panel meeting in Örebro, Sweden, in May 2009. The panel also developed a TASC lesion classification for infrapopliteal arteries (Jaff et al. 2015). However, consensus regarding the revascularization strategy was not achieved, mainly due to lacking definitive high-level evidence with an emphasis on clinical and economic effectiveness upon which to base treatment decisions (Beard 2008, Schanzer and Conte 2010).

The choice of treatment method remains highly individual, as it depends on many factors: the patient’s current status and comorbidities, the location of the anatomic disease, the available technical resources, and the clinician’s experience.
Table 2. TASC classification of femoropopliteal lesions and treatment recommendations

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description of the lesion</th>
<th>Recommended treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TASC A</strong></td>
<td>- Single stenosis ≤ 10cm or occlusion ≤ 5cm in length</td>
<td>Endovascular</td>
</tr>
<tr>
<td><strong>TASC B</strong></td>
<td>- Multiple lesions (stenosis/occlusion), each ≤5cm</td>
<td>Endovascular</td>
</tr>
<tr>
<td></td>
<td>- Single stenosis/occlusion ≤15cm not involving the below-knee arteries</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Single or multiple lesions in the absence of continuous tibial vessels to improve inflow</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Heavily calcified occlusion ≤ 5cm in length</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Single popliteal stenosis</td>
<td></td>
</tr>
<tr>
<td><strong>TASC C</strong></td>
<td>- Multiple stenosis or occlusion totaling &gt;15cm with/without heavy calcification</td>
<td>Open surgery for low-risk patients, Endovascular for high-risk patients</td>
</tr>
<tr>
<td></td>
<td>- Recurrent stenosis or occlusion that needs treatment after two endovascular interventions</td>
<td></td>
</tr>
<tr>
<td><strong>TASC D</strong></td>
<td>- Chronic total occlusions of the CFA/SFA</td>
<td>Open surgery</td>
</tr>
<tr>
<td></td>
<td>- Chronic total occlusions of the popliteal artery and proximal trifurcation vessel</td>
<td></td>
</tr>
</tbody>
</table>

1.1.10.1 *Infrainguinal bypass surgery (IBS)*

Open surgical bypass has been a standard operation for the vascular surgeon for over 40 years. A fundamental principle of IBS is to provide unimpeded arterial runoff to the selected outflow vessel (Conte 2009). IBS is relevant in cases with extensive superficial femoral artery disease, particularly or extensive infrapopliteal lesions (Norgren et al. 2007).

There is a significant amount of literature studying the outcome for the great saphenous vein conduit with various operative techniques (in situ, transposed, non-reversed, and
reversed), especially in cases of extensive PAD in the infrapopliteal region (Van Damme 2004, Schanzer et al. 2007, Conte 2009). In the absence of a good-quality saphenous vein, another autologous vein (lesser saphenous vein, arm veins) or prosthetic material can be used as the conduit (Barsches et al. 2013). The patency of the different vein configurations is comparable and the choice primarily depends on anatomic circumstances and the surgeon’s preferences (Shah et al. 1995, Schanzer et al. 2007). The prosthetic grafts are more dependent on outflow resistance and less tolerant of the low-flow state, which leads to poorer patency in long-term follow-up (Johnson and Lee. 2000, Twine and McLain 2010). Furthermore, an increased risk of wound infection in patients with ischemic tissue loss leads surgeons to prefer an autologous vein, as the resistance is better than in prosthetic grafts (Bandyk 2008).

A large randomized trial, Edifoligide for the Prevention of Infrainguinal Vein Graft Failure (PREVENT III), reported the primary patency, survival, and limb salvage rates at 1-year follow up—61%, 83.8%, and 88.5%, respectively. Peri-procedure mortality occurred in 2.7%, and surgical wound complications were reported in 4.8% of the patients (Conte et al. 2006). The only randomized trial comparing bypass surgery to angioplasty in patients with severe ischemia, BASIL, reported equal results of amputation-free survival at 6 months. However, over a follow-up of 3 to ≥5 years, the surgical group demonstrated a numerical trend towards better overall and amputation-free survival (Adam et al. 2005, Bradbury et al. 2010).

Bypass surgery is usually reserved for complex and extensive lesions in patients whose health status suggests a >2-year survival (Jaff et al. 2015). Two trials, The Best Endovascular versus Best Surgical Therapy in patients with CLI (Menard and Farber 2014) and BASIL II, have been launched and will bring answers to the question of whether optimal surgery for selected patients with a good-quality saphenous vein is a better choice than endovascular therapy.

1.1.10.2 Percutaneous transluminal angioplasty (PTA)

Endovascular revascularization of a short femoral occlusion was first attempted in 1964 (Dotter and Judkins); the treatment of infrapopliteal disease has been reported since the early 1990s (Iyer et al.). PTA is a mini-invasive procedure, which can be performed under local anesthesia. Using the luminal or subintimal technique, the atherosclerotic lesion is crossed with a guide wire, and a balloon on catheter, with or without a supporting mesh (stent), is passed over into the desired position. Inflating the balloon leads to the dilatation of the stenosed or occluded vessel.

The rapid evolution of technology available for endovascular treatment (sheaths, catheters, wires, balloons, stents, drug-device combinations, debulking tools such as cryoplasty or excisional atherectomy) allows technical success even with the most complex of anatomies (Laird et al. 2006, DeRubertis et al. 2007, Jaff et al. 2015), which has led to the widespread adoption of an endovascular-first approach for CLI patients (Jaff et al.2015). The technical success rates differ from study to study, mainly due to the heterogeneous definition of a successful procedure (Diehm et al. 2007). A meta-analysis including 30 studies reported a pooled estimate of technical success of 89% and a 3-year limb salvage rate of 82.4%
(Romiti et al. 2008). The most common procedural complications are bleeding from the puncture site followed by a pseudoaneurysm, as well as thrombosis, distal embolization, dissections, vessel perforation, renal failure, and cardiac complications; the complication rate was reported to be 7%–10% (DeRubertis et al. 2007, Romiti et al. 2008).

Despite the minimal invasion, the procedure is not without risk, especially in patients with co-morbidities—the reported early death rate is 2%–3% (Adam et al. 2005, Haider et al. 2006, Conrad et al. 2009). Furthermore, there is a high rate of restenosis, 50% at one year (Mlekush et al. 2002) and 65% at two years (Haider et al. 2006), resulting in a need for repeated interventions, which may be seen as the major limitation of endovascular revascularization.

1.1.10.3 Hybrid procedure
A strategy combining endovascular and open surgical techniques is gaining popularity. In many cases, it may offer better inflow, which is managed by endovascular treatment and followed by infrainguinal surgical revascularization. The typical case example would be combined aortoiliac and infrainguinal disease (Chang et al. 2008, Aho and Venermo 2012).

1.1.10.4 Major amputation
Major amputation is defined as an amputation above the ankle level, and despite the advances and aggressive treatment of CLI, the amputation rates are still high (Abou-Zamzam et al. 2006). Primary amputation as an alternative to revascularization is indicated in cases where a functional limb can no longer be provided. This applies mainly to non-ambulatory elderly patients with flexion contractures, life-threatening infections, extensive necrosis that has destroyed the foot, or cases where rest pain cannot be controlled (Nehler et al.2003, Norgren et al. 2007).

A primary amputation is to be considered as the most appropriate treatment for patients with severe co-morbidities or very limited chance of successful revascularization due to extended PAD (Biancari et al. 2000, Abou-Zamzam et al. 2007). Secondary major amputation is performed if vascular reconstruction is no longer possible or if the limb continues deteriorate despite the presence of patent reconstruction (Norgren et al. 2007).

1.1.10.5 Pharmacotherapy
Several pharmacological agents (prostanoids, vasodilators, antiplatelet drugs, anticoagulants, and vasoactive drugs) as an alternative to amputation have been tried in cases where revascularization is not technically possible (Norgren et al. 2007). Prostanoids resulted in an improvement of the clinical picture regarding rest-pain relief, ulcer healing, and amputation-free survival (Rufolo et al. 2010), as it protects the endothelium by preventing platelets and activating leucocytes. However, the long-term effectiveness and safety for the patients is not known; a frequent occurrence of side effects such as facial flushing, nausea, vomiting, and diarrhea has been reported (Ruffolo et al. 2010). Therefore, prostanoids are rarely used (Norgren et al. 2007).
1.1.11 Diabetic foot ulcer (DFU)

Every year, over a million diabetic patients lose their limb; in other words, an amputation is performed every 20 seconds in the world as an outcome of this debilitating disease (Boulton et al. 2005). Approximately 80% of diabetes-related lower extremity amputations are preceded by a foot ulcer (Hingorani et al. 2016), which develops in 25% of diabetic patients during their lifetime (Gregg et al. 2004).

Risk factors for ulcer development include: neuropathy, severe PAD (CLI), foot deformity, limited ankle range of motion, high plantar foot pressures, minor trauma, previous ulceration or amputation, and visual impairment (Armstrong et al. 2003, Boulton 2004, Morbach et al. 2004, Bowling et al. 2015). Because of the multifactorial process of DFU formation, they are usually categorized into three groups: neuropathic, ischemic, and neuroischemic (Norgren et al. 2007). An increasing proportion of diabetic patients with an ischemic or neuroischemic wound as opposed to neuropathic wounds alone have been observed (Morbach et al. 2012, Hingorani et al. 2016). The current estimation shows that an ischemic component presents in at least 65% of DFUs (Hinchliffe et al. 2012, Armstrong et al. 2013), and the multicenter prospective European Study Group on Diabetes and the Lower Extremity, EURODILE, observed that the presence of PAD increases the annual amputation and mortality rate from 2% to 8% and from 3% to 9%, respectively (Prompers et al. 2008).

Therefore, all patients with diabetes and an ulcer should be referred to vascular centers for an evaluation of foot perfusion. A general practitioner can only obtain information on pulse pulsation and ABI values, which have been proven unreliable for PAD diagnosis in patients with diabetes. The presence of pedal pulses does not conclusively exclude the presence of PAD (Rivers et al. 1990, Collins et al. 2006), and ABI may be falsely elevated as a result of non-compressible arteries affected by medial calcinosis (Aerden et al. 2011, Alvaro-Afonso et al. 2015). A superior reliability has been shown for TP and TcPO2 measurements (Brownrigg et al. 2016, Hinchliffe et al. 2016, Sonter et al. 2015); the effectiveness of one non-invasive bedside investigation, however, proved insufficient for the detection of PAD among diabetic patients (Brownrigg et al. 2016, Hinchliffe et al. 2016).

Therefore, regardless of the measurements, if there is any doubt concerning the blood perfusion, imaging should be performed to evaluate the severity of the atherosclerosis. The recent guidelines of the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine (Figure 2) recommend a revascularization procedure (endovascular or surgical) in patients with a DFU and PAD (Hingorani et al. 2016). The choice of revascularization method is subject to the same problems as with non-diabetic CLI patients. The trend towards an endovascular first strategy is observed (Faglia et al. 2005), even though clear evidence favoring endovascular therapy over open bypass in terms of better clinical outcome is lacking (Hinchliffe et al. 2012). More importantly, the presence or absence of infection is crucial in the planning of revascularization. An infection increases the likelihood of a non-healing ulcer three-fold (Prompers et al. 2008), and an aggressive control of the infection
with appropriate antibiotics and thorough debridement must therefore be administered before or during any type of revascularization (Prompers et al. 2008, Lipsky et al. 2013).


**DFU Prevention:**
- Patient education
- Annual foot exam
- Glycemic control (A1c<7%)
- Therapeutic footwear
- Semmes-Weinstein monofilaments test
- ABI at the age 50
- Vascular risk factor management

**Patient develop ulcer**

**Access for ischaemia, infection and neuropathy**
- ABI + TcPo2
- Probe to bone + plain X-ray

**Clinically significant PAD**
- Revascularization (either surgical bypass or endovascular therapy)
**Angiosome theory**

In 1987, Taylor and Palmer introduced the angiosome concept in their anatomical study. The angiosome research was conducted due to evolving tissue transfer techniques in plastic and reconstructive surgery. The authors’ aim was to investigate the important aspects of microvascular anatomy and identify complicated flaps that would not develop necrosis due to a lack of arterial supply.

The investigation was performed on fresh cadavers that showed no obvious evidence of PAD. After an injection of the perfusion mixture and careful dissection, a three-dimensional subtraction picture was taken of the vascular network (Taylor and Palmer 1987, Inoue and Taylor 1996, Taylor and Pam 1998, Houseman and Taylor 2000).

1.1.12 Definition

An angiosome is defined as a 3-dimensional unit of each tissue layer between the skin and bone supplied and drained by specific vessels (Taylor and Palmer 1987).

Taylor et al. described in detail the angiosomal distribution of the upper extremity and neck (Inoue and Taylor 1996, Houseman and Taylor 2000); the lower extremity was mapped from the gluteal area to the ankle region (Taylor and Pam 1998,). Attinger et al. (2001, 2006) focused on the distribution in the foot and concluded on the existence of 6 angiosomes, each supplied by one of the crural arteries and its terminal branches, Figure 3. The angiosomal areas and source vessels are described as follows:

**Angiosome 1:** Covers the dorsal surface of the foot; the source artery is the arteria dorsalis pedis (ADP).

**Angiosome 2:** Covers a small surface of the lateral malleolus; is supplied by the arteria peronealis (AP).

**Angiosome 3:** Covers the lateroposterior and plantar surface of the heel; the source artery is the terminal branch of AP, the calcaneal branch.

**Angiosomes 4–6:** The main source artery is the arteria tibialis posterior (ATP). As the ATP continues distally to the foot, it splits into three main branches supplying three separate angiosomes: 4) the mediodorsal and plantar heel via its calcaneal branch, 5) the medial instep via the medial plantar artery, and 6) the lateral instep and the plantar forefoot via the lateral plantar artery. Figure 3A

Due to multiple arterial variations (Adachi and Hasebe 1928), another distribution of angiosomes in the plantar side of foot has been observed (Attinger et al. 2006). The lateral plantar artery can be the source for the lateral instep and forefoot, including only the region of the fifth toe until the lateral side of the second toe (angiosome 4), which leaves the medial plantar artery to be the source of the medial instep and plantar forefoot from the hallux to the medial side of second toe (angiosome 3). Figure 3B (Attinger et al. 2006)
Some studies even consider the hallux and the medial side of the second toe as a separate angiosome—angiosome 7 (Houlind and Christensen 2013). The source artery of the hallucal angiosome varies depending on the anatomy. A Japanese study conducted on 100 cadavers showed that the hallux is supplied either by the ADP (the first dorsal metatarsal branch), the lateral plantar artery (the first plantar metatarsal branch) or, secondarily, the medial plantar artery (the hallucal branch) (Hamada et al. 1993). Figure 3C.

Figure 3. Angiosomal distribution (A) and its variations (B, C)

a, the angiosome of ATA; b, the angiosome of AP including the lateral malleolar angiosome (2); c, the angiosome of ATP. 1, dorsal angiosome, source = ADP; 2, lateral malleolar angiosome, source = AP; 3, dorsolateral and plantar angiosome, source = calcaneal branch of the AP; 4, dorsomedial and plantar angiosome, source = calcaneal branch of ATP; 5, medial plantar instep and forefoot angiosome, source = medial plantar artery; 6, lateral plantar foot and forefoot angiosome, source = lateral plantar artery and 7, angiosome of the hallux and medial side of the second toe, source = dorsal metatarsal artery (78%), plantar metatarsal artery (22%).
Several arterial-arterial connections exist between the angiosomes: 1) the so-called “true anastomosis”, i.e. arteries with no change in caliber—e.g., the plantar arch connecting to the pedal arteries and allowing uninterrupted blood flow to the entire foot despite the occlusion of one of the crural arteries (Taylor and Palmer 1987, Attinger et al. 2006, Taylor et al. 2013); and 2) the so-called “choke vessels”, i.e. small arteries with a decrease in caliber requiring a period of ischemia to open (Aydin and Mavili 2003, Taylor et al. 2013). However, those connections may be occluded by progressing PAD, especially in diabetic patients whose mid- and small-sized arteries occlude due to medial calcinosis. Therefore, the tissue of the angiosome with a compromised source artery can suffer from severe ischemia. (Clemens and Attinger 2010)

Most tissue covers two or more angiosomes by receiving arterial blood from another angiosomal source artery—e.g., the plantar heel supplied by the calcanear branch of both the ATP and AP. Therefore, it is hard to identify an exact junction zone (border) between the angiosomes as it usually occurs within the tissue (Taylor and Pam 1998,).

1.1.13 Application in treatment of CLI
Although the literature states that pulsatile flow to the correct region of the foot is necessary to heal ischemic tissue loss (Treiman et al. 2003, Hughes et al. 2004), defining such a region for revascularization remains under debate.

After the introduction of the angiosome concept, the idea of so-called “angiosome-targeted” revascularization—the restoration of blood flow directly to the angiosome affected by the ischemic wound—appeared among vascular surgeons (Alexandrescu et al. 2008, Neville et al. 2009, Iida et al. 2010).

They hypothesized that direct revascularization may result in a better clinical outcome as the perfusion of the ischemic foot, provided by the open line from the abdominal aorta to the source artery, should be higher than after indirect revascularization, a procedure on an artery that is not related to the affected angiosome. Direct revascularization according to ulcer location has been defined as presented in Table 3.

<table>
<thead>
<tr>
<th>Ulcer location</th>
<th>Direct revascularization</th>
<th>Indirect revascularization</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Forefoot</strong></td>
<td>ATA/ADP ± ATP/plantar arteries</td>
<td>AP</td>
</tr>
<tr>
<td>(angiosome 1,5,6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dorsum of the foot</strong></td>
<td>ATA/ADP</td>
<td>ATP, AP</td>
</tr>
<tr>
<td>(angiosome 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Medial instep</strong></td>
<td>ATP with patency of medial plantar</td>
<td>AP, ATA, ADP</td>
</tr>
<tr>
<td>(angiosome 5)</td>
<td>plantar artery</td>
<td></td>
</tr>
<tr>
<td><strong>Lateral instep</strong></td>
<td>ATP with patency of lateral plantar</td>
<td>AP, ATA, ADP</td>
</tr>
<tr>
<td>(angiosome 6)</td>
<td>plantar artery</td>
<td></td>
</tr>
<tr>
<td><strong>Heel</strong></td>
<td>ATP/AP</td>
<td>ATA, ADP</td>
</tr>
<tr>
<td>(angiosome 3,4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lateral malleolus</strong></td>
<td>AP</td>
<td>ATA, ADP, ATP</td>
</tr>
<tr>
<td>(angiosome 2)</td>
<td></td>
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</table>

An exception to obtaining direct revascularization in the case of tissue loss located in the forefoot and heel was made due to multiple vascularizations of the angiosomes (Attinger et al. 2006, Neville et al. 2009). Alexandrescu et al. (2013) described a different approach of angiosome-targeted revascularization for lesions located in the forefoot and heel, presenting the ATP as the first choice of arterial reconstruction.

et al. 2015), or both groups supported the superiority of angiosome-oriented revascularization (Kabra et al. 2013, Lejay et al. 2014). The two recent meta-analyses, including a total of 15 retrospective studies, also reported that wound healing and limb salvage is better in favor of direct revascularization, especially in patients with diabetes (Biancari and Juvonen 2014, Bosanquet et al. 2015).

Despite the promising results, the importance of the concept has been contradicted. For example, in revascularization by surgical bypass, Varela et al. (2010) and Rashid et al. (2013) suggested that the wound healing more likely depends on the quality of pedal arch rather than the angiosome-targeted approach. One of the main flaws of the angiosome concept is the unclear definition of direct revascularization in cases where the wound spreads over several angiosomes, which is the case in most of the diabetic patients (Aerden et al. 2014). Only Iida et al. (2012, 2013 and 2014) mention this problematic issue in their studies, without a consensus, however. In their study from 2012, direct revascularization is explained as a procedure on all source arteries of the angiosomes involved in the lesion, yet in the studies published in 2013 and 2014, it is defined as revascularization of the angiosome with the largest surface involved in the wound.

Furthermore, a randomized trial that would compare direct versus indirect revascularization and take collateral vascularization into account is lacking. The likelihood that such a trial would be forthcoming is minimal due to the complexity of randomizing patients based on concurrent angiography and the need to provide the safest form of revascularization. Therefore, it has been suggested that before a widespread adoption of angiosome-guided revascularization as a novel technique in vascular reconstruction, more clinical evidence in the form of well-structured, prospective studies must become available (Sumpio et al. 2013).

1.1.14 Wound healing

The available evidence favors angiosome-oriented revascularization in terms of better wound healing rates. In the initial series including 52 distal bypasses, the ulcer failed to heal in 9% of the cases in the direct group versus 38% in the indirect group (Attinger et al. 2006). A larger series of 539 consecutive CLI patients with Rutherford 5–6 ischemia and isolated below-knee arterial lesions who had neither diabetes mellitus or an infected wound, Iida et al. (2014) observed a higher complete wound healing rate at 1 year in the direct group as adjusted for propensity score, 75% vs. 64%, in the indirect group. The other two studies reporting data from a propensity-score-matched analysis showed a trend towards a better wound healing rate after direct revascularization (HR 0.72, 95% CI 0.50–1.04, $I^2$ 29%) (Azuma et al. 2012, Södeström et al. 2013).

Among diabetic patients, Alexandrescu et al. (2008) were the first to report the benefit of the angiosome concept analyzing 98 diabetic patients with CLI and a foot ulcer (Wagner grade 1–4). The study reported complete wound healing in 79% of the treated limbs. The propensity score analysis in a study by Södeström et al. (2013) adjusted for diabetes, age, sex, CAD, gangrene, and estimated glomerular filtration rate <30mL/min/1.73m^2 or dialysis, showed a significantly better wound healing rate in the direct group (HR 1.97; 95% CI 1.34–2.90; p<0.001). In a multicenter retrospective study from Japan, the median
wound healing time among diabetic patients with an isolated infrapopliteal arterial lesion was 146 days, and indirect revascularization was one of the independent predictors of delayed wound healing (Shiraki et al. 2015).

The meta-analysis by Biancari and Juvonen (2014) reported that the risk of an unhealed wound was significantly lower after direct revascularization (HR 0.64, 95% CI 0.52–0.8, $I^2$ 0%, four studies included) compared to indirect revascularization. Data regarding wound healing in the meta-analysis by Bosanquet et al. (2014) included 11 papers and showed a significantly improved wound healing rate after direct revascularization, with an odds ratio of 0.40 (95% CI 0.29–0.54, p < 0.00001), in both the bypass and the endovascular group.

1.1.15 Limb salvage

In the field of vascular surgery, leg salvage means the preservation of a functional foot without the need for a leg prosthesis (Tefera et al. 2005). A clear benefit of direct revascularization is not as evident in regard to this matter as in wound healing rates.


An analysis of 6 studies (Varela et al. 2010, Blanes et al. 2011, Alexandrescu et al. 2011, Iida et al. 2012, Lejay et al. 2013 and Kabra et al. 2013) resulted in pooled leg salvage rates at 86.2% in the direct group vs. 77.8% in the indirect group 1 year, and 84.9% vs. 70.1%, respectively, at 2 years (Biancari and Juvonen 2014). The benefit of angiosome-guided revascularization in terms of leg salvage was confirmed among diabetic patients (HR 0.48, 95% CI 0.31–0.75, $I^2$ 0%, three studies included) (Biancari and Juvonen 2014).

1.1.16 Amputation-free survival (AFS)

Amputation-free survival defined as the avoidance of major amputation is reported in only 3 studies (Iida et al. 2012 and 2014, Söderström et al. 2013). The study by Iida et al. (2014) reports no significant difference between direct and indirect revascularization, 60% vs. 57% at 24 months, respectively. AFS at 1 year in patients with diabetes whose wound healed was 41% in the direct group compared to 26% in indirect group. However, the overall AFS at 1 year showed no difference between the groups, 65% for direct vs. 61% for indirect (Söderström et al. 2013). The meta-analysis reported only a trend towards better results in favor of angiosome-oriented revascularization (HR 0.81, 95% CI: 0.61–1.06, $I^2$ 25%) (Biancari and Juvonen 2014).
AIMS OF THE PRESENT STUDY

The main purpose of this study was to analyze the use of the angiosome concept in the treatment of patients with CLI and tissue loss (Rutherford 5–6). (Figure 4)

The specific aims were to:

1. Evaluate of the feasibility of angiosome-guided endovascular revascularization and assess the topography of the ischemic tissue loss in relation to the angiosome concept. (I)

2. Compare and investigate the factors influencing the complete healing time of ischemic tissue lesions, including the healing of the incisional wounds, according to the angiosome concept (II, III).

3. Compare the clinical outcome of angiosome-guided bypass surgery and endovascular therapy of the infrapopliteal arteries as a first-line revascularization strategy in patients with CLI and tissue loss (II), and in diabetic patients with CLI and tissue loss (III).

4. Evaluate which of the two existing angiosome-targeted definitions is more usable in clinical practice (IV).
Figure 4. Flowchart showing the design of each study

Patients with CLI and tissue loss that were treated by infrapopliteal revascularization between 2008-2013

N=1306

Study I
Patients treated in 2012
N=160

Number of vessels Possible to revascularize?

N=1  N=2  N=3

DR performed?

Study II
Patients treated between 2010-2013
N=744

Study III
Diabetic patients treated between 2008-2013
N=545

Study IV
Patients treated between 2010-2013
N=658

DR performed?

Reason?

Definition A
Definition B

Wound healing? Leg salvage?
PATIENTS AND METHODS

The Institutional Review Board of Helsinki University Hospital (HUH) approved all of the studies. From hospital records, we retrospectively gathered 1306 patients with CLI and tissue loss who underwent infrapopliteal revascularization at our clinic between January 2008 and December 2013. Our prospective HusVasc registry provided the following information: indication for revascularization, specific revascularization details, type of local surgery, and patient demographics (Table 4). The comorbid diseases were verified as follows:

- CAD - documented coronary artery disease, previous coronary bypass surgery, history of myocardial infarction, angina pectoris or ischemic changes on ECG,
- CVD - history of stroke or transient ischemic attack,
- Pulmonary disease - chronic obstructive pulmonary disease or asthma,
- Diabetes mellitus - hyperglycemia requiring diet or medication,
- Hypertension - medication for hypertension or blood pressure repeatedly > 160/90 mmHg,
- Dyslipidemia - medication for hyperlipidemia or fS-cholesterol > 5 mmol/L or S-LDLcholesterol > 3 mmol/L,
- Heart failure - documented heart failure,
- Smoking - current smoking.

HusVasc registry data were manually crosschecked with the patient records, and missing data was retrieved, such as wound healing time and amputation status. Statistics Finland provided the data on the patients’ deaths.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Study I (%)</th>
<th>Study II (%)</th>
<th>Study III (%)</th>
<th>Study IV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of included patients</td>
<td>160</td>
<td>744</td>
<td>545</td>
<td>658</td>
</tr>
<tr>
<td>Age: median (range)</td>
<td>76 (42–93)</td>
<td>74 (39–102)</td>
<td>73 (39–94)</td>
<td>74 (39–102)</td>
</tr>
<tr>
<td>Female</td>
<td>60 (37.59)</td>
<td>274 (36.8)</td>
<td>170 (31)</td>
<td>246 (37.3)</td>
</tr>
<tr>
<td>Smoking</td>
<td>20 (12.5)</td>
<td>108 (14.5)</td>
<td>69 (12.7)</td>
<td>96 (14.6)</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>20 (12.5)</td>
<td>83 (11.2)</td>
<td>49 (9.9)</td>
<td>77 (11.7)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>59 (36.9)</td>
<td>216 (29.0)</td>
<td>136 (25)</td>
<td>202 (30.7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>98 (61.3)</td>
<td>468 (62.9)</td>
<td>516 (94.7)</td>
<td>417 (63.4)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>88 (55.0)</td>
<td>191 (25.7)</td>
<td>148 (27.2)</td>
<td>166 (25.2)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>107 (66.9)</td>
<td>461 (62.0)</td>
<td>545 (100.0)</td>
<td>412 (62.6)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>63 (39.4)</td>
<td>270 (36.3)</td>
<td>224 (41.1)</td>
<td>242 (36.8)</td>
</tr>
<tr>
<td>Hearth failure</td>
<td>24 (15.0)</td>
<td>91 (12.2)</td>
<td>62 (11.4)</td>
<td>85 (12.9)</td>
</tr>
<tr>
<td>CRP: median (range)</td>
<td>51 (3–263)</td>
<td>52 (3–315)</td>
<td>48 (2–315)</td>
<td>52 (3–315)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>28 (17.5)</td>
<td>104 (14.0)</td>
<td>74 (13.6)</td>
<td>94 (14.3)</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate: median (range)</td>
<td>50 (7–60)</td>
<td>39 (4–60)</td>
<td>43 (4–60)</td>
<td>39 (4–60)</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>14 (8.8)</td>
<td>44 (5.9)</td>
<td>41 (7.5)</td>
<td>42 (6.4)</td>
</tr>
<tr>
<td>Kidney transplantation</td>
<td>7 (4.4)</td>
<td>15 (2.0)</td>
<td>15 (2.8)</td>
<td>12 (1.8)</td>
</tr>
<tr>
<td>Type of revascularization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endovascular revascularization</td>
<td>162 (100)</td>
<td>503 (67.3)</td>
<td>316 (58)</td>
<td>445 (67.6)</td>
</tr>
<tr>
<td>Surgical revascularization</td>
<td>-</td>
<td>241 (32.7)</td>
<td>229 (42.0)</td>
<td>213 (32.4)</td>
</tr>
</tbody>
</table>
**Wound location**
The location and severity of the tissue loss was obtained by reviewing our clinical notes. Photographs were taken in one in eight cases. We adopted the general scheme of angiosomal distribution to evaluate the number of affected angiosomes (Figure 5).

**Figure 5. General scheme of angiosomal distribution** (Attinger et al. 2006, Alexandrescu et al. 2012, Iida et al. 2010, Varela et al. 2010, Sumpio et al. 2013, Söderström et al. 2013)
a, angiosome of ATA; b, angiosome of AP; and c, angiosome of ATP. 1, Dorsal angiosome; 2, angiosome of lateral malleolus; 3, dorsolateral and plantar angiosome; 4, dorsomedial and plantar angisome; 5, medial plantar instep and forefoot angiosome; 6, lateral plantar foot and forefoot angiosome
Run-off arteries
We retrospectively reviewed the preoperative angiograms (studies I–IV); the status of leg and foot arteries was quantified according to the Society for Vascular Surgery (SVS)/International Society for Cardiovascular Surgery (ISCVS) scoring system of angiographic appearance as follows: 0, normal or minimal evidence of disease; 1, 20%–49% stenosis; 2, 50%–99% stenosis; 2.5, occluded less than halfway; 3, occluded through most of the length. The infrapopliteal arteries that scored SVS/ISCVS 2, 2.5, and 3 with patent outflow were considered candidates for endovascular treatment (studies I–IV).

After analyzing the number of arteries feasible for endovascular treatment, we divided the patients into 3 groups: group 1 (G1) representing patients with only one crural artery suitable for revascularization, group 2 (G2) containing patients with two crural arteries fulfilling the conditions for angioplasty, and group 3 (G3) containing patients with all three crural arteries as an option for revascularization (Study I).

In cases of patients who underwent surgical bypass and whose angiograms were missing, the outflow arteries and leg status were evaluated based on the preoperative MRA (study II–IV).

Angiosome-targeted revascularization
We defined direct revascularization as a procedure on the artery supplying the angiosome affected by an ischemic lesion. For the lesions located in the forefoot or heel, revascularization of any of the affected angiosomes was accepted into the direct group (definition A). In cases of a foot ulcer spreading over several angiosomes and not located in the forefoot or heel, direct revascularization was defined as a procedure on the artery supplying the largest surface of the angiosome involved in the lesion. If the patient suffered from multiple foot ulcers located in separate angiosomes, all affected angiosomes had to be revascularized in order to count as direct revascularization (studies I–IV).

In the last study (study IV), we compared the conventional definition of direct revascularization to a different one presented in the literature (definition B), targeting only the posterior tibial artery/plantar arteries for a lesion located in the forefoot or heel (Alexandrescu 2013).

In order to evaluate whether direct revascularization was achieved, all postoperative angiograms were restrospectively reviewed and manually crosschecked with the HusVasc register (I–IV).

Wound care
The wound care protocol depended on the characteristics of each lesion: surgical debridement of necrotic tissue, revision of infected ulcers, and skin graft application in cases of impossible primary or secondary closure. Patients with infected wounds received adequate antimicrobial therapy (II–IV).
Follow-up
After the revascularization, patients remained under routine surveillance at the outpatient clinic. A vascular nurse carried out duplex ultrasound examinations of the revascularized artery and followed the foot status; a vascular surgeon was consulted if necessary (e.g. signs of re-stenosis, non-hwaling or worsening of the wound) After PTA, the visits were scheduled at 1, 3, and 6 months, and in the case of a bypass graft at 1, 3, 6, and 12 months. If the wound remained open at the last routine duplex surveillance, the patient continued to visit to the outpatient clinic until the wound was fully healed. The follow-up ended if the patient underwent a new infrainguinal bypass due to a failure of the primary intervention (endovascular or surgical), a major amputation due to a non-healing foot ulcer, or if the patient died (II–IV).

Outcome measures
We evaluated 1) how often an ischemic lesion is located in one angiosome and 2) the reasons for not achieving direct revascularization in cases where the angiosomal artery was suitable for endovascular therapy (study I). We compared the outcomes of direct and indirect surgical versus endovascular revascularization (studies II–III), and direct versus indirect revascularization using the two definitions (study IV). The primary outcome measures were wound healing and leg salvage (II–IV).

Statistical analysis
For statistical analysis, we used SPSS v. 22.0 statistical software (II–IV) and MS Excel 2003 (study I). Continuous variables were reported as mean and standard deviation, and nominal variables as absolute number and percentage. Pearson’s Chi-square test, Fisher’s exact test and the Mann-Whitney U test were used for univariate analysis. Long-term outcome was assessed by Kaplan-Meier’s method with the log-rank test and the Cox proportional hazards method (II–IV).

Differences between study groups were adjusted by estimating a propensity score. The propensity score was calculated by means of non-parsimonious logistic regression. (IV) Hosmer-Lemeshow’s test was used to assess the regression model fit. The calculated propensity score was employed for one-to-one matching as well as to adjust for other variables in estimating their impact on the postoperative outcome. One-to-one propensity score matching between study groups was performed according to a caliper width equal to 0.2 times the standard deviation of the calculated propensity score’s logit. Outcome in the propensity-matched pairs was evaluated by Kaplan-Meier’s methods as well as the Cox regression method. P<0.050 was considered statistically significant (II).
RESULTS

The feasibility of the angiosome concept (I)

A total of 161 legs (160 patients) undergoing primary infrapopliteal angioplasty in 2012 were included. The wound(s) interfered with more than one angiosome in 75.8% of the cases. (Figure 6)

Figure 6. The number of affected angiosomes in 161 legs
Of all the affected extremities, 33% had only one crural artery suitable for revascularization (G1); the remaining 2 arteries were either without any sign of disease ($n = 17$) or occluded ($n = 36$) with no patent outflow (Figure 7).

Figure 7. The number of arteries suitable for revascularization
Out of the overall 161 extremities, direct flow was achieved in 98 (60.9%) legs and indirect flow via non-targeted revascularization in 63 (39.1%) legs. Direct revascularization was possible in 129 (80.1%) legs and performed in 98 (75.9%) cases. The reasons behind the 31 cases where direct PTA was possible but not performed were as follows: (1) it was attempted without success ($n = 9$) and another vessel was then revascularized; (2) the occlusion was long ($n = 14$), resulting in revascularization of another vessel; and (3) unknown reason ($n = 8$). Table 5.

Table 5. Feasibility and success rate of direct revascularization (DR) in relation to the number of crural arteries suitable for PTA.

<table>
<thead>
<tr>
<th>Number of arteries suitable for PTA</th>
<th>DR possible (%)</th>
<th>DR achieved (%)</th>
<th>DR not achieved</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DR not achieved</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Failed (%)</td>
<td>Long occlusion (%)</td>
<td>Unknown (%)</td>
</tr>
<tr>
<td>1</td>
<td>33 (62.3)</td>
<td>26 (78.8)</td>
<td>2 (6.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 (9.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 (6.1)</td>
</tr>
<tr>
<td>2</td>
<td>76 (86.4)</td>
<td>57 (75.0)</td>
<td>6 (7.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8 (10.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 (6.6)</td>
</tr>
<tr>
<td>3</td>
<td>20 (100.0)</td>
<td>15 (75.0)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 (15.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Total</td>
<td>129 (80.1)</td>
<td>98 (75.9)</td>
<td>9 (7.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14 (10.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8 (6.2)</td>
</tr>
</tbody>
</table>
Interestingly, a higher chance that the angiosomal artery will be a candidate for revascularization was observed with wound(s) spreading over 2 or 3 angiosomes (Table 6).

**Table 6. Feasibility and success rate of direct revascularization (DR) in relation to the number of affected angiosomes.**

<table>
<thead>
<tr>
<th>Number of affected angiosomes</th>
<th>DR possible (%)</th>
<th>DR achieved (%)</th>
<th>DR not achieved</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Failed (%)</td>
</tr>
<tr>
<td>1</td>
<td>27 (69.2)</td>
<td>22 (81.5)</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>2</td>
<td>65 (86.7)</td>
<td>47 (72.3)</td>
<td>6 (9.2)</td>
</tr>
<tr>
<td>3</td>
<td>35 (83.3)</td>
<td>29 (82.9)</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>1 (25.0)</td>
<td>0 (0.0)</td>
<td>1 (100.0)</td>
</tr>
<tr>
<td>5</td>
<td>1 (100.0)</td>
<td>0 (0.0)</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>129 (80.1)</td>
<td>98 (75.9)</td>
<td>9 (7.0)</td>
</tr>
</tbody>
</table>
The importance of the angiosome concept—bypass surgery vs. PTA (II)
The comparison of direct and indirect revascularization between the revascularization methods comprises 744 consecutive patients; 503 underwent PTA and 241 surgical bypass between January 2010 and June 2013. Out of all cases, direct revascularization was achieved in 55%.

1.1.17 Wound healing
The Cox proportional hazards analysis revealed that direct revascularization (p=0.036, HR 1.294, 95%CI 1.017–1.647), bypass surgery (p<0.0001, HR 1.791, 95%CI 1.412–2.272), C-reactive protein ≤ 10 mg/dL (p=0.005, HR 1.416, 95%CI 1.110–1.806), and fewer affected angiosomes (p=0.024, HR 0.854, 95%CI 0.744–0.979) improved the healing potential. When adjusted for the number of affected angiosomes and C-reactive protein ≤ 10 mg/dL, direct bypass was associated with a significantly higher rate of wound healing than indirect angioplasty (p<0.001, HR 2.265, 95%CI 1.605–3.196). Interestingly, indirect bypass also achieved better wound healing rates than PTA independently of the angiosome-oriented strategy (p=0.001, HR 1.890, 95%CI 1.292–2.766) (Figure 8)

Figure 8. Adjusted Cox proportional hazards estimates of wound healing according to treatment method and angiosome-targeted revascularization (p<0.0001).
1.1.18 Leg salvage
Direct revascularization was associated with a trend towards improved leg salvage (p=0.065, Table 7). The Cox proportional hazards analysis demonstrated that an increasing number of affected angiosomes (p<0.0001, HR 1.439, 95%CI 1.206–1.717), atrial fibrillation (p=0.028, HR 1.499, 95%CI 1.046–2.149), C-reactive protein > 10 mg/dL (p=0.002, HR 1.952, 95%CI 1.271–2.997), CKD class 5 (p=0.002, HR 2.285, 95%CI 1.354–3.856), and indirect revascularization (p=0.014, HR 1.531, 95%CI 1.088–2.154) were independent predictors of major amputation.

1.1.19 Propensity score
A total of 252 pairs were included in the analysis. Direct revascularization was associated with significantly better leg salvage and a trend towards improved wound healing (Table 7). When adjusted for propensity score and treatment method (bypass surgery vs. angioplasty), direct revascularization was associated with a significantly higher wound healing rate (p=0.046, HR 1.295, 95%CI 1.005–1.668). Direct revascularization yielded a significantly lower risk of major amputation (p=0.010, HR 0.637, 95%CI 0.452–0.897) and better amputation-free survival (p=0.037, HR 0.788, 95%CI 0.630–0.986) in the propensity-score-adjusted analysis (Figure 9).
Figure 9. Propensity-score-adjusted hazard of major amputation according to angiosome-targeted and non-targeted revascularization (p=0.010, HR 0.637, 95%CI 0.452–0.897).
Table 7. One-year follow-up outcome of patients who underwent direct or indirect infrainguinal revascularization for critical limb ischemia. Data are reported for the overall population and propensity-score-matched pairs.

<table>
<thead>
<tr>
<th>Outcome end point</th>
<th>Overall series</th>
<th>Propensity-matched pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Indirect 336 pts</td>
<td>Direct 408 pts</td>
</tr>
<tr>
<td>Wound healing</td>
<td>69.2%</td>
<td>72.1%</td>
</tr>
<tr>
<td>Survival</td>
<td>77.1%</td>
<td>78.5%</td>
</tr>
<tr>
<td>Leg salvage</td>
<td>77.5%</td>
<td>82.7%</td>
</tr>
<tr>
<td>Amputation-free survival</td>
<td>62.2%</td>
<td>66.5%</td>
</tr>
</tbody>
</table>
Role of the angiosome concept in diabetic patients—bypass vs. PTA (III)
The cohort consists of 545 patients, 316 of whom underwent PTA and 229 surgical bypass between January 2008 and December 2013. The overall success rate of direct revascularization was 59.4%.

1.1.20 Wound healing
The overall wound healing rate at one-year follow-up was 60.3%. The highest rate was achieved after direct bypass (77%) and the worst after indirect PTA (52%). The Cox proportional hazards analysis showed that number of affected angiosomes<3 (HR 1.37, 95%CI 1.01–1.84) and Type of the procedure were independently associated with wound healing, and the poorest wound healing was seen after indirect PTA (p=0.001; Figure 10).

Figure 10. Kaplan-Mayer estimates for wound healing in diabetic patients who underwent infrapopliteal revascularization
1.1.21 Leg salvage
The overall amputation rate at one year was 25.1%. Cox proportional hazards analysis indicated that haemodialysis compared to patients with no haemodialysis (HR 2.55, 95%CI 1.49-4.38), C-reactive protein≥10 mg/dL (HR 2.05, 95%CI 1.45–2.90), atrial fibrillation (HR 1.54, 95% CI 1.05-2.26) and number of affected angiosomes>3 (HR 1.75, 95%CI 1.24-2.46) were significantly associated with poor leg salvage. The indirect PTA predicted poorest leg survival (Figure 11).

Figure 11. Kaplan-Mayer estimates for leg salvage in patients who underwent infrapopliteal revascularization, (p=0.041).
The outcome difference of the two angiosome-targeted definitions (IV)
This retrospective study included 658 consecutive patients who underwent either PTA or surgical bypass of the infrapopliteal arteries between January 2010 and July 2013. When applying definition A—targeting any involved angiosome in the wound that is located in the forefoot or the heel—367 (55.8%) cases fulfilled the criteria for direct revascularization. Applying definition B—targeting only ATP as the source of the forefoot and heel angiosomes—the number of cases with direct revascularization decreased significantly, n=198 (30.1%, p<0.05).

Unadjusted actuarial analysis showed that, irrespective of the definition (A or B), direct revascularization yielded better wound healing and leg salvage rates when compared to indirect revascularization. A propensity-score-adjusted analysis showed that, when definition A was adopted, direct revascularization was associated with significantly better wound healing and leg salvage rates, whereas when definition B was applied, direct revascularization was associated only with significantly better wound healing (Table 8).

The prognostic ability of definition A was confirmed in a Cox proportional hazards analysis as adjusted for diabetes, estimated glomerular filtration rate, C-reactive protein, revascularization method, the number of affected angiosomes, and the presence of an intact pedal arch (Table 8). When both direct revascularization definitions were included in the latter regression model, only definition A was associated with better wound healing (p=0.040, HR 1.286, 95%CI 1.012–1.635) and a lower risk of major amputation (p=0.038, HR 0.698, 95%CI 0.497–0.980).
Table 8. The outcome of patients who underwent direct infrapopliteal revascularization according to the two different definitions. Data are reported for the adjusted propensity-score-matched pairs and Cox proportional hazard

<table>
<thead>
<tr>
<th>Outcome end-points</th>
<th>Definition A</th>
<th>Definition B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p-value</td>
<td>HR (95%CI)</td>
</tr>
<tr>
<td>Wound healing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propensity score</td>
<td>0.044</td>
<td>1.291 (1.007–1.656)</td>
</tr>
<tr>
<td>Cox proportional hazard</td>
<td>0.037</td>
<td>1.294 (1.016–1.648)</td>
</tr>
<tr>
<td>Major amputation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propensity score</td>
<td>0.047</td>
<td>0.706 (0.501–0.996)</td>
</tr>
<tr>
<td>Cox proportional hazard</td>
<td>0.044</td>
<td>0.703 (0.847–0.990)</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propensity score</td>
<td>0.938</td>
<td>0.990 (0.761–1.286)</td>
</tr>
<tr>
<td>Cox proportional hazard</td>
<td>0.356</td>
<td>0.886 (0.685–1.146)</td>
</tr>
</tbody>
</table>
DISCUSSION

Critical limb ischemia significantly affects the quality of life and mortality, and the number of patients suffering from end-stage PAD is raising due to the aging of the population and the increasing incidence of DM (WHO, Armstrong et al. 2014). Therefore, the need to treat CLI due to leg rest pain or a foot ulcer has become more frequent over the last decade. Advancing endovascular technologies opened the possibility for a less-invasive treatment of extensive lesions, even in infrapopliteal segments. Historically, achieving one open line to the foot was considered satisfactory, but studies showed that the random reconstruction of a single infrapopliteal artery yields a poor clinical outcome as it resulted in refractory ulcers with a relatively high amputation rate of 10%–18% (Khan et al. 2009, Blevins and Schneider 2010).

The angiosome concept, originally implemented in plastic surgery, brought anatomical insight into the clinical strategy of CLI treatment. Focusing on revascularizing the feeding artery of the ischemic angiosome led to the hypothesis of improved wound healing and leg salvage rates. Neville et al. (2009) observed 48 patients with non-healing ulcers and found that applying the angiosome concept resulted in better outcomes. After this finding, extensive research has been carried out on angiosome-targeted revascularization. A meta-analysis of 15 recent studies showed that the main benefits of direct revascularization prevail in improved wound healing rates; the effect of direct revascularization in terms of better leg salvage rates, however, was lost in certain sensitivity analyses (Bosanquet et al. 2014).

One of the main criticisms of the angiosome concept remains the nonexistence of randomized trials and the inconsistent methodologies of the papers that are all retrospective—non-standardized decision-making concerning direct revascularization may result in the selection of different vessels, constituting a serious source of bias (McCallum and Lane 2014, Bosanquet et al. 2014). While direct revascularization is achieved in approximately 60% of the patients in open surgery groups (Azuma et al. 2012, Rashid et al. 2013, Lejay et al. 2014, Kret et al. 2014), the range of technical success in endovascular groups differs dramatically. A study by Södeström et al. (2013) that investigated diabetic patients with a foot ulcer reports a technical success rate of 48%, while Alexandrescu et al. (2008) achieved direct revascularization in 82% of diabetics. The significant difference in technical success rates between the studies can be explained by the diversity of skills between individual vascular centers as well as different angiosome-targeted approaches. The mean success rate of achieved direct revascularization among EVT is roughly 62% (Fosacecca et al. 2013, Acin et al. 2014, Alexandrescu et al. 2008 and 2011, Oshima et al. 2013, Iida 2013 and 2014, Söderström et al. 2013, Shiraki et al. 2015, Zheng et al. 2016).

We investigated the feasibility of angiosome-targeted revascularization in patients that were selected for primary endovascular therapy, and our results showed that one in three patients had only one crural artery suitable for the EVT. In about one third of the cases where the source artery was suitable for EVT, the approach was attempted without success and an easier artery then selected; in roughly half of the cases, it was not even attempted
because of a long lesion. Furthermore, in only 24% of the patients, the wound was isolated to a single angiosome. In the literature, the definition of direct revascularization for wounds spreading over several angiosomes is scarce and inconsistent. Iida et al. (2013, 2014) targeted the largest surface affected; due to the dual blood supply of the heel and digits, however, it is difficult to correctly define the direct revascularization of these regions. Two different approaches of direct revascularization for wounds spreading over the forefoot and heel are available, as mentioned in methodology. We compared the definitions in our last study, and, although both were associated with better wound healing, targeting only the posterior tibial artery did not predict leg salvage when the risk factors were adjusted with propensity score analysis. Furthermore, it was less successful clinically, as the technical success rate of achieved direct flow was 30%, due to the fact that the clinician was limited to only one crural artery as an option for direct revascularization.

Based on our findings described above, it seems that, with a treatment policy of “endovascular first,” we have to accept a certain number of indirect revascularizations, instead of treating suitable cases with targeted bypass which yielded the best clinical outcomes in our second and third study. Additionally, we found that indirect EVT yields the poorest leg salvage and was, together with wound infection, an independent predictor of major amputation, while an angiosome-targeted strategy in surgical bypass seems to be of less value.

In 1999, Berceli et al. studied 400 patients who underwent dorsal pedal bypass and reported similar wound healing rates for heel and forefoot ulcers (Berceli et al. 1999). This contradicts the angiosome-targeted hypothesis, but can be explained by the importance of the collaterals between each angiosome. Attinger et al. (2006) stated that the angiosome of the heel is unique by its dual supply that has arterial-arterial connections with the ADP. Therefore, the wound healing can be similar as the angiosome of the heel receives retrograde blood flow via this true anastomosis. Varela et al. (2010) addressed the overlooked importance of collaterals and reported that revascularization through collateral vessels yielded similar results as direct revascularization: the respective wound healing rates at 12 months were 92% vs. 85%, and the respective leg salvage rates at 24 months, 93% vs. 88%. Also, Rashid et al. (2013) reported the superiority of the quality of the pedal arch when compared to the angiosome-targeted strategy in bypass surgery. However, in the case of absent collaterals, direct revascularization seems to be the best option, as also shown herein in our results. The collateral vascularization is poor if the patient suffers from diabetes and end-stage kidney disease, and these patients were shown to benefit significantly from direct revascularization (Iida et al. 2013, Shiraki et al. 2015). We found similar results in our third study, where direct revascularization was associated with better wound healing (HR 1.4, 95%CI 1.5–1.9, p<0.0001) and where hemodialysis together with indirect PTA was an independent predictor of major amputation (HR 2.62, 95%CI 1.53–4.45).

In order to evaluate the differences between surgical and endovascular revascularization, we performed a subanalysis among patients who underwent angiosome-targeted revascularization (study II). In this comparison, bypass surgery was associated with a better wound healing rate than endovascular revascularization, but the leg salvage rates were similar. This comparison included a limited number of patients, and the results can be
seen only as preliminary. Also, when comparing the revascularization method in diabetic patients (study III), the results show that wound healing was better in bypass surgery, independently of the angiosome-orientation, rather than in PTA.

We can only speculate the possible reasons of the differences between the surgical and endovascular method. After bypass, an arterial line with a good diameter perfuses the distal part of the lower limb, while after PTA, the size of the arterial line is smaller. Furthermore, many patients presented on angiograms with non-significant femoral-popliteal or multiple stenoses in revascularized artery; these were usually bypassed in open surgery group. Therefore, we can hypothesize that the pressure impact after direct PTA may be smaller compared to bypass due to higher resistance in revascularized artery. When non-significant stenoses are in series the effect on resistance is roughly cumulative (Flangian et al. 1977, Karayanakos et al. 1977). The poor outcome after indirect PTA is easier to understand—in these cases, the distal arterial tree is probably very sick and allows only limited revascularization, but, in cases of indirect bypass, the pressure still changes more dramatically.

When choosing between surgical and endovascular revascularization, we have to bear in mind the completely different levels of invasiveness of the procedures. Especially the majority of diabetic patients are elderly fragile women, in whom the aim of as non-invasive an intervention as possible leads to a shorter hospital stay and quicker rehabilitation. Despite the evolution in endovascular technology, long infrapopliteal occlusions remain challenging for endovascular therapy due to the high risk of failure and a need for repeated revascularization attempts. Failure of endovascular therapy, usually after two PTAs, results in a delay of surgical bypass revascularization. Such a delay, mainly in diabetics, may lead to poorer leg salvage rates (Noronen et al. 2016). Therefore, in cases of long infrapopliteal occlusions where direct EVT is not feasible, the change in policy to opt for surgical bypass first seems to bring benefits to the patient, unless the patient is too fragile or has other contraindications for the surgical intervention. We must bear in mind the different pathophysiology of a diabetic foot and the high tendency for infection in diabetic patients. When treating DFUs, revascularizing the foot alone is not enough for wound healing as the ischemia does not necessarily play the main role in developing the tissue defect. Therefore, cooperation between specialties with adequate treatment and follow-up of all factors playing a role in DFU development is needed to achieve the best results for diabetic patients.

Without a doubt, a well-planned, prospective study with a precisely defined wound location and size, high-quality angiograms with information on collaterals as well as the patency of the pedal arch, and careful wound healing follow-up is needed to confirm the usefulness of the angiosome concept in the treatment of CLI and tissue loss.
Limitations of the study

A number of limitations may affect the results—all the studies are retrospective, which may lead to potential selection bias in terms of the ischemic tissue lesion determination according to the angiosome concept. Even though the data has been drawn from our prospectively collected database, the identification of the precise ulcer location can be difficult in some cases (I–IV). Furthermore, the existence of dual supply to the heel and forefoot, resulting in more than one angisomal distribution, may influence the determination, because we were unable to distinguish the dominant source artery based on preoperative images (I–IV). Also, the determination of the correct angiosome affected by ischemia cannot be made based on a DSA or MRA, as information on the microcirculation and perfusion of the skin is necessary for a complete determination. The other limitation remains in the definition of targeted revascularization in cases where the ulcer spans several angiosomes; due to unclear methodology in previous publications, adjustments were made in studies II–IV, which could affect the results. Moreover, in some cases, the evaluation of angiograms may be problematic due to the poor quality of the images as regards limitations in the examined region (I–IV). DSAs were not available in all cases in the surgical group, and MRAs were used instead, therefore rendering the information on the pedal arteries and the quality of the pedal arch poorer (II–IV). The wound healing time in studies II–IV may have been overestimated, because the status was checked intermittently and the wound care protocol was not standardized and took place in a number of other facilities outside HUCH.
CONCLUSION

Based on this thesis, the following conclusions can be drawn:

1) The angiosome concept is feasible for the majority of patients treated with an endovascular approach, although only 24% of the tissue lesions are localized to one angiosome only.

2) The factors that are associated with worse wound healing time are: a number of affected angiosomes of >3, CRP>10 and indirect PTA.

3) Surprisingly, there was no significant difference between the patient cohorts in study II and III (diabetic patients only). Therefore, observing the angiosome concept in the decision-making seems to bring better wound-healing and leg salvage rates, especially in endovascular therapy. In bypass surgery, however, the concept seems to be of less value, and the artery with the best runoff should be selected as the outflow artery.

4) It seems that, if the wound spreads over more than one angiosome in the location of the forefoot or heel, any angiosome involved in the wound (definition A) can be targeted to achieve a better clinical outcome.

In summary, critical limb ischemia presenting as a foot ulcer is a serious impairment of a patient’s health status and requires the quick re-establishment of arterial blood supply. The tissue lesion affects several angiosomes in the majority of the cases, which seems to be one of the main factors delaying wound healing time. Furthermore, in such cases, consensus needs to be achieved concerning the accurate definition to standardize the methodology. Based on our findings, the angiosome concept plays an important role in endovascular treatment, as indirect revascularization leads to the poorest clinical outcomes.
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