Chapter 1

General introduction
Peripheral arterial disease (PAD) is the development of stenoses or occlusions in arteries of the lower extremity. The stenoses and occlusions are caused by an accumulation of cholesterol and other lipid compositions, known as atherosclerosis, in the inner wall of arteries. These atherosclerotic plaques can protrude into the vessel lumen and limit the blood flow to distal tissues. These chronic obstructive lesions can cause pain in the legs and nonhealing wounds that significantly reduce the quality of life. In so-called vulnerable plaques, there is a high risk of plaque rupture, which is one of the leading causes of acute limb ischemia and other acute cardiovascular events.

The aetiology of atherosclerosis in peripheral arteries is complex and multifactorial. One of the strongest risk factors for PAD is diabetes mellitus. An estimated 20% to 30% of patients with PAD have concomitant diabetes mellitus. This combination is unfavorable because diabetes accelerates PAD and worsens disease severity. The presentation of PAD differs in patients with diabetes, with more severe involvement of below-the-knee arteries and a high prevalence of long, calcified occlusions. This combination challenges treatment and increases the risk of tissue loss.

PAD and diabetes are both independent risk factors of tissue loss. However, the cause of tissue loss in patients with diabetes is not only vascular but also includes nonvascular factors such as neuropathy and biomechanical deformities. Tissue loss in these patients includes diabetic foot ulcers, of which the risk of amputation is high due to the complex aetiology.

A recent study investigated the amputation trends for patients with lower-extremity ulcers due to diabetes and PAD in the United States. Amputation rates rose between 2010 and 2013 in patients with diabetes mellitus and in those with concomitant PAD and diabetes. The latter had the highest amputation rates, with an increase of 17%, from 24 per 100 patients in 2010 to 28 per 100 patients in 2013. A similar increase in lower-extremity amputation rates of 16% was observed in the Netherlands between 2009 and 2017. An increase in lower-extremity amputations was also observed in other European countries, including Germany, United Kingdom, and Sweden, between 2009 and 2017.

The risk of amputation in patients with PAD highly depends on its severity. In patients with ischemic pain at rest or tissue loss for more than 2 weeks, the risk of amputation is 12-times higher than in patients with mild symptoms. Therefore, patients with these severe symptoms are known as chronic limb-threatening ischemia (CLTI) patients. One of the major concerns is that CLTI will develop in approximately 11% of patients, in whom the risk of amputation is as high as 22% at 1 year, when left untreated. Revascularization is the cornerstone for the treatment of CLTI patients and can increase limb salvage rates by 60%. However, there remains a subgroup of CLTI patients in which conventional revascularization techniques are no longer possible due to the extensiveness of the disease. These patients are characterized as no-option CLTI patients and have a 30% risk of undergoing an amputation.
at 1 year, when left untreated. Because of the increased risk of amputation in patients with diabetic foot ulcers, CLTI, and no-option CLTI, the need to improve outcomes in these patient populations is pressing.

**DIABETIC FOOT ULCER**

Diabetic foot disease is one of the most serious complications of diabetes mellitus. It is a cause of major suffering and financial costs for the patient and a considerable burden on the patient’s family and heath care professionals. As a result of the frequent involvement of CLTI, patients with a diabetic foot ulcer are often considered as a subgroup of CLTI and require different treatment due to the multifactorial pathophysiology. A diabetic foot ulcer is usually the result of multiple factors, including increased biomechanical stress, impaired skin perfusion, loss of sensation, and external trauma. This combination is dangerous: abnormal biomechanical loading or even an ill-fitting shoe will not be noticed because of the loss of sensation. As a result, a small foot ulcer can develop but remains unnoticed due to the loss of sensitivity in the foot. Eventually, it can develop into an infected ulcer, which is an alarming situation: The 1-year major amputation rate for these patients has been reported to be as high as 44%.

**CHRONIC LIMB-THREATENING ISCHEMIA**

The term CLTI represents the spectrum of patients with and without diabetes who have PAD of sufficient severity to delay wound healing and increase amputation risk. The Global Vascular Guidelines define CLTI as the presence of PAD including one or more of the following symptoms:

- Ischemic rest pain with abnormal haemodynamic parameters (ankle-brachial index < 0.4, absolute toe pressure < 30 mmHg, or transcutaneous partial pressure of oxygen < 30 mmHg);
- Diabetic foot ulcer or any lower-limb ulceration present for at least 2 weeks;
- Gangrene involving any segment of the lower limb or foot.

CLTI patients are at high risk of amputation due to the severity of atherosclerotic lesions, the presence of nonhealing ulcers, or the existence of gangrene. Further, clinically significant lesions in infrapopliteal and inframalleolar arteries are typical for CLTI patients. These lesions are more difficult to treat compared with femoropopliteal lesions due the lack of outflow, resulting in a high restenosis and reocclusion rate.

Revascularization is fundamental for limb salvage in CLTI patients and can be performed surgically or by an endovascular approach. The latter has the advantage of the avoidance of general anesthesia, absence of surgical wounds in a malperfused area, and less perioperative morbidity and mortality. However, higher 12-month reintervention rates are observed after endovascular revascularization compared with bypass surgery.
The higher treatment success by bypass surgery does not outweigh its drawbacks, however, which include an increased risk of postoperative infection, a lengthy hospital stay, and the need to use high-care units. Therefore, endovascular therapy has become the treatment of choice for infrapopliteal disease in the frail CLTI patient population.

This has resulted in an evolution of newer technologies to improve the success rates of endovascular revascularization in infrapopliteal arteries. Specifically, drug-coated balloons and drug-eluting stents have been a focus of development because their antiproliferative drugs limit the chance of restenosis. Two recent meta-analyses showed a tendency toward improved results with drug-eluting stents compared with bare-metal stents in patency, freedom from target lesion revascularization, and major amputation at 1 year. However, the long-term outcomes were similar. The benefits of percutaneous transluminal angioplasty by a drug-coated balloon also remain controversial.

Several adjunctive endovascular devices, such as atherectomy, cryoplasty, cutting balloons, and laser, have been shown to be feasible and safe in the infrapopliteal arteries but have failed to show superior efficacy compared with conventional, less expensive therapies and are therefore not recommended. However, there is still an urgent need for the development of techniques and devices, because not all lesions are successfully treated by plain old balloon angioplasty due to the inability to cross severely calcified lesions and failure to open the arterial lumen. Besides, there is a subgroup of no-option CLTI patients who cannot be treated by conventional revascularization techniques.

**NO-OPTION CLTI**

There remains a group of CLTI patients in whom, despite all of revascularization treatments available, revascularization by bypass or an endovascular approach is not an option. In these patients, the total distal vascular bed is affected, including the foot arteries, which is known as the “desert foot.” A bypass would not be possible in these patients due to the lack of an open outflow artery, and endovascular treatment is deemed unfeasible because the whole arterial tract is affected. Thus, these patients are characterized as no-option CLTI patients.

Amputation rates in no-option CLTI patients are high. A recent study found a major amputation rate of 30% at 1 year, when left untreated. Different nonrevascularization treatments have been proposed to improve limb salvage rates in this severely affected patient population. These treatments include spinal cord stimulation, lumbar sympathectomy, intermittent pneumatic compression, hypobaric oxygen therapy, and the use of prostanoids. Studies have shown that spinal cord stimulation has some effect on pain relief, and an 11% reduction in the amputation rate was reported. Intermittent pneumatic compression might also have an effect on pain relief and the limb salvage rate, but in carefully selected patients. Other treatment modalities have failed to demonstrate improved limb salvage rates and are therefore not recommended.
In 1912, Halstead and Vaughan tried venous arterialization as an alternative revascularization technique for these patients. In this technique, a connection is made between the artery and the vein to transport the arterialized blood through the disease-free venous bed to the foot. However, the procedure was not successful due to the construction of fistula in the groin and the thoughts that the veins would be destroyed by the arterial pressure. After Sheil successfully treated patients by a venous arterialization using valve destruction in 1977, the technique became the subject of research, and different variations followed. Currently, venous arterialization can be performed several ways, including a surgical, open approach, a hybrid approach, and a fully percutaneous approach. The percutaneous deep venous arterialization (pDVA) procedure was first described in 2017. This pilot study showed promising results with limb salvages rates of 71% at 1 year, despite the early primary patency loss at a median of 3 months after the procedure. Owing to the novelty of the procedure, many aspects of pDVA remain undetermined, including periprocedural and postprocedural management, several of which are explored in part 3 of this thesis.

**AIM AND OUTLINE OF THIS THESIS**

The aim of this thesis is (i) to determine the effects of outpatient treatment strategies on limb salvage and ulcer healing in patients with a diabetic foot ulcer, (ii) to evaluate the outcomes of various endovascular therapies of infrapopliteal lesions in CLTI patients, and (iii) to assess the pDVA technique, its outcomes, and the optimal postoperative management and surveillance strategies.

In **Chapter 2**, we investigated the effect of treatment with and without antibiotics in patients with clinically uninfected foot ulcers in the outpatient clinic. Data on the antibiotics given, the microbiological profile of the ulcers, and reasons to prescribe antibiotic treatment for clinically uninfected ulcers were collected. The wound healing rate, limb salvage rate, amputation-free survival and overall survival were analyzed and compared between the two groups.

In **Chapter 3**, outcomes in 188 diabetic foot ulcers after treatment by a multidisciplinary outpatient team approach were compared with 148 diabetic foot ulcers treated by a vascular surgeon only. Predictors for major amputation were evaluated, and differences in wound healing and limb salvages rates were analyzed and compared.

In **Chapter 4**, the feasibility and outcomes of below-the-ankle angioplasty was assessed by a meta-analysis of 10 previously published studies. Outcomes of additional below-the-ankle angioplasty were compared with below-the-knee angioplasty alone.

In **Chapter 5**, the safety, feasibility, and effectiveness of a high-pressure noncompliant balloon were evaluated for the treatment of long infrapopliteal, calcified lesions. The effectiveness was assessed by evaluating its results on limb salvage, wound healing, overall survival, and freedom from clinically driven target lesion reintervention.
In Chapter 6, a meta-analysis was conducted to study the outcomes of plain old balloon angioplasty versus angioplasty with a drug-coated balloon in below-the-knee lesions. Rates of limb salvage, overall survival, restenosis, and target lesion revascularization were pooled and compared.

In Chapter 7, we used porcine arteries obtained from the abattoir to develop and validate an ex vivo flow model in which the effects of endovascular revascularization techniques on the arterial wall can be tested in a standardized, physiological environment.

Chapter 8 describes the technique and technical aspects of pDVA and reports its outcomes from a pilot study of 7 patients.

In Chapter 9, duplex measurements in patients after pDVA were assessed to determine cutoff values for the presence and absence of stenosis or occlusions in the arteriovenous circuit.

Chapter 10 further evaluated the peak systolic velocity and volume flow as measured by duplex in patients after pDVA to create a prediction model to estimate the risk of future stenosis or occlusions.

In Chapter 11, the postoperative management of patients after pDVA was reviewed, and an expert opinion was provided. Reviewed subjects included postoperative medication, edema occurrence and treatment, pain management, patency assessment, reintervention techniques, a staged amputation strategy, and appropriate wound care.

Chapter 12 provides a summary of this thesis and discusses future perspectives.
REFERENCES


PART 1

OUTPATIENT MANAGEMENT OF PATIENTS WITH A DIABETIC FOOT