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2014

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*Citation for published version (APA):*

Elgzyri, T. (2014). *Outcome of Ischaemic Foot Ulcers in Patients with Diabetes, with or without Revascularization*. [Doctoral Thesis (compilation), Translational Muscle Research]. Diabetes and Endocrinology.

*Total number of authors:*

1

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# Outcome of Ischaemic Foot Ulcers in Patients with Diabetes, with or without Revascularization

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Department of Clinical Sciences  
Diabetes and Endocrinology  
Lund University 2014



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DOCTORAL DISSERTATION

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To be defended at Lilla Aulan, Jan Waldenströms gata 5, Skåne University  
Hospital SUS, Malmö. Tuesday, September 23<sup>rd</sup> 2014, at 09.00 am.

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Organization LUND UNIVERSITY Department of Clinical Sciences, Malmö		Document name DOCTORAL DISSERTATION	
		Date of issue 2104-08-15	
Author(s) Targ Elgzyri		Sponsoring organization	
Title and subtitle: Outcome of ischaemic foot ulcers in patients with diabetes, with or without revascularization.			
Abstract: <p>The aim of the studies presented in this thesis was to study patients with diabetes and severe peripheral arterial disease (PAD) in regard to outcomes of foot ulcers, factors related to outcomes, and occurrences of new ulcerations and amputations following healing of the initial ulcer.</p> <p>Patients with diabetes and a foot ulcer, consecutively presenting at a multidisciplinary foot centre, with a systolic toe pressure &lt;45 mm Hg or an ankle pressure &lt;80 mm Hg, were prospectively included, followed up according to a predefined program, and offered vascular intervention when applicable. All patients had continuous follow-up until healing or death, irrespective of the vascular intervention.</p> <p>In total (n=1,151), 36% of patients healed primarily, 16% healed after minor amputation, 13% healed after a major amputation, and 27% died unhealed. At the end of the study, there was a dropout rate of 5%, and 3% of patients were still in treatment. In patients considered not feasible for revascularization (n=602), 38% healed primarily, 12% healed after minor amputation, 17% healed after major amputation, and 33% died unhealed. Comorbidities, the severity of PAD, and the extent of tissue involvement were strongly related to a low probability for ulcer healing, irrespective of revascularization. Angioplasty or reconstructive vascular surgery increased the probability of healing. The time to revascularization after admittance to a diabetic foot centre was also related to the probability of healing without major amputation.</p> <p>After healing from a previous ischaemic ulcer, 34% of patients developed a new ulceration in the same foot within the observation time. Twenty-two percent of patients who developed new ulcers had an amputation before healing from the new ulcers. Lesser maximal tissue destruction during the previous ulcer and open reconstructive vascular surgery were related to a lower risk of new ulcerations. Patients with diabetes and ischaemic foot ulcers had a median survival time of 33 months.</p> <p>In conclusion, this thesis has shown that a substantial number of patients with diabetes, foot ulcers, and severe PAD can heal without a major amputation. The probability of ulcer healing was strongly related to comorbidity, the extent of tissue involvement, and the severity of PAD. Patients with diabetes and ischaemic foot ulcers not feasible for revascularisation are not excluded from healing without major amputation. Not only revascularization per se, but also the timing of revascularization increased the probability of healing without a major amputation. Following healing, these patients had a high risk of developing new ulcers. The extent of tissue involvement of a previous ulcer and reconstructive vascular surgery affected the risk of developing new ulcers.</p>			
Key words: Diabetic foot ulcers, PAD, outcomes			
Classification system and/or index terms (if any)			
Supplementary bibliographical information		Language: English	
ISSN and key title: 1652-8220		ISBN: 978-91-7619-028-9	
Recipient's notes		Number of pages	Price
		Security classification	

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Lund University, Faculty of Medicine Doctoral Dissertation Series 2014:99

ISBN 978-91-7619-028-9

ISSN 1652-8220

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Printed in Sweden by Media-Tryck, Lund University  
Lund 2014



KLIMATKOMPENSERAT  
PAPPER



**“And mankind have not been given of knowledge except a little”**  
*The Holy Quran, surat Al Isrá, verse (85)*

To the memory of my beloved parents ***Mabroka*** and ***Khalil***

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# List of original papers

This thesis is based on the following studies, which will be referred to by their Roman numerals.

- I. Apelqvist J, Elgzyri T, Larsson J, Löndahl M, Nyberg P, Thörne J. **Factors related to outcome of neuroischemic/ischemic foot ulcer in diabetic patients.** J Vasc Surg. 2011;53:1582-8.
- II. Targ Elgzyri, Jan Larsson, Johan Thörne, Karl-Fredrik Eriksson and Jan Apelqvist. **Outcome of ischemic foot ulcer in diabetic patients not available for vascular intervention.** Eur J Vasc Endovasc Surg. 2013;46:110-7.
- III. Targ Elgzyri, Jan Larsson, Per Nyberg, Johan Thörne, Karl-Fredrik Eriksson and Jan Apelqvist. **Early revascularization after admittance to a diabetic foot center affects the healing probability of ischemic foot ulcer in patients with diabetes.** Eur J Vasc Endovasc Surg 2014 Aug 5. doi: 10.1016/j.ejvs.2014.06.041. [Epub ahead of print].
- IV. Targ Elgzyri, Jan Larsson, Per Nyberg, Johan Thörne, Karl-Fredrik Eriksson and Jan Apelqvist. **Reconstructive vascular surgery and extent of tissue involvement in previous foot ulcers are related to lower risk of new ulceration in patients with diabetes and severe peripheral arterial disease.** (*Submitted*).

# Abbreviations

ABI	Ankle brachial index
ACE	Angiotensin converting enzyme
ACR	Albumin-to-creatinine ratio
ARB	Angiotensin II receptor blockers
CI	Confidence interval
CLI	Critical limb ischaemia
CTA	Computed tomography angiography
CVD	Cardiovascular disease
DCCT	Diabetes control and Complications Trial
DFU	Diabetic foot ulcer
DM	Diabetes mellitus
DMO	Diabetic macular oedema
DN	Diabetic nephropathy
DPN	Diabetes peripheral neuropathy
DR	Diabetic retinopathy
DSA	Digital subtraction angiography
DUS	Duplex ultrasound
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
HbA1c	Glycosylated haemoglobin A1c
HBO	Hyperbaric oxygen therapy
HR	Hazard ratio
IC	Intermittent claudication
IWGDF	International Working Group on the Diabetic Foot
NPDR	Non-proliferative diabetic retinopathy
NPWT	Negative pressure wound therapy
MODY	Maturity-onset diabetes of the young
PAD	Peripheral arterial disease
PTA	Percutaneous transluminal angioplasty
MRA	Magnetic resonance angiography
OR	Odds ratio

PDR	Proliferative diabetic retinopathy
RCT	Randomized controlled trials
TBI	Toe brachial index
TcPO2	Transcutaneous pressure of oxygen
UKPDS	United Kingdom Prospective Diabetes Study

# Definitions

The following definitions, except for minor and major amputation, are according to the international consensus on the diabetic foot by the International Working Group on the Diabetic Foot (IWGDF):<sup>1</sup>

**Superficial ulcer:** Full thickness lesion of the skin not penetrating any structure deeper than the dermis.

**Deep ulcer:** Full thickness lesion of the skin penetrating below the dermis to subcutaneous structures involving fascia, muscle, tendon or bone.

**Necrosis:** Devitalized (dead) tissue.

**Gangrene:** Necrosis of the skin and underlying structures with irreversible damage.

**Debridement:** Removal of callus or dead tissue.

**Infection:** A pathological state caused by invasion and multiplication of microorganisms in tissues accompanied by tissue destruction and/or a host inflammatory response.

**Superficial infection:** An infection of the skin not extending to any structure below the dermis.

**Deep infection:** An infection that extends deeper than the dermis, with evidence of abscess, septic arthritis, osteomyelitis, septic tenosynovitis or necrotizing fasciitis.

**Cellulitis:** An infection of the skin manifested by one or more of the following signs and symptoms: induration, erythema, warmth, pain or tenderness.

**Osteitis:** Infection of the bone cortex without evidence of involvement of bone marrow.

**Osteomyelitis:** Infection of the bone, with evidence of involvement of the bone marrow.

**Amputation:** Surgical removal of the whole or part of a limb including its distal end, through the distal interphalangeal joint of a toe, or higher.

**Minor amputation:** Any amputation at or distal to the talo-crural joint.<sup>2,3</sup>

**Major amputation:** Any amputation proximal to the talo-crural joint.<sup>2,3</sup>

**Re-amputation:** Repeated amputation in the same limb to correct an unhealed amputation.

**New amputation:** Amputation in a limb with a healed previous resection.

**Wagner grade classification of foot ulcers:**<sup>4</sup>

Grade 1: Superficial Ulcer

Grade 2: Ulcer extension involving ligament, tendon, joint capsule or fascia, no abscess or osteomyelitis

Grade 3: Deep ulcer with abscess or osteomyelitis

Grade 4: Gangrene to a portion of the forefoot

Grade 5: Extensive gangrene of the foot

# Abstract

The aim of the studies presented in this thesis was to study patients with diabetes and severe peripheral arterial disease (PAD) in regard to outcomes of foot ulcers, factors related to outcomes, and occurrences of new ulcerations and amputations following healing of the initial ulcer.

Patients with diabetes and a foot ulcer, consecutively presenting at a multidisciplinary foot centre, with a systolic toe pressure <45 mm Hg or an ankle pressure <80 mm Hg, were prospectively included, followed up according to a predefined program, and offered vascular intervention when applicable. All patients had continuous follow-up until healing or death, irrespective of the vascular intervention.

In total (n=1,151), 36% of patients healed primarily, 16% healed after minor amputation, 13% healed after a major amputation, and 27% died unhealed. At the end of the study, there was a dropout rate of 5%, and 3% of patients were still in treatment. In patients considered not feasible for revascularization (n=602), 38% healed primarily, 12% healed after minor amputation, 17% healed after major amputation, and 33% died unhealed. Comorbidities, the severity of PAD, and the extent of tissue involvement were strongly related to a low probability for ulcer healing, irrespective of revascularization. Angioplasty or reconstructive vascular surgery increased the probability of healing. The time to revascularization after admittance to a diabetic foot centre was also related to the probability of healing without major amputation.

After healing from a previous ischaemic ulcer, 34% of patients developed a new ulceration in the same foot within the observation time. Twenty-two percent of patients who developed new ulcers had an amputation before healing from the new ulcers. Lesser maximal tissue destruction during the previous ulcer and open reconstructive vascular surgery were related to a lower risk of new ulcerations. Patients with diabetes and ischaemic foot ulcers had a median survival time of 33 months.

In conclusion, this thesis has shown that a substantial number of patients with diabetes, foot ulcers, and severe PAD can heal without a major amputation. The probability of ulcer healing was strongly related to comorbidity, the extent of tissue involvement, and the severity of PAD. Patients with diabetes and ischaemic foot ulcers not feasible for revascularisation are not excluded from healing without

major amputation. Not only revascularization *per se*, but also the timing of revascularization increased the probability of healing without a major amputation. Following healing, these patients had a high risk of developing new ulcers. The extent of tissue involvement of a previous ulcer and reconstructive vascular surgery affected the risk of developing new ulcers.

# Introduction

## Diabetes mellitus

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Diabetes mellitus is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action or both.<sup>5</sup> This results in high glucose levels that cause unique eye, kidney and nerve complications, and an increased risk of cardiovascular disease.

Diabetes is a rapidly growing problem worldwide, making it one of the most challenging health problems in the 21st century. The total number of people with diabetes is projected to rise from 382 million adults in 2013 to 592 million adults by 2035.<sup>6</sup> This is further aggravated by changing population demographics, urbanization, and lifestyle factors.

There are mainly four types of diabetes.<sup>5</sup> **Type 1 diabetes**, which is less common, is caused by the autoimmune destruction of the insulin-producing  $\beta$ -cells in the islets of Langerhans in the pancreas, thereby leading to an absolute insulin deficiency and a requirement for insulin administration. **Type 2 diabetes**, the most common type of diabetes, makes up to 85–95% of diabetes cases. It is caused by a relative insulin deficiency, which result from a progressive insulin secretion defect in the context of insulin resistance.

**Other specific types** of diabetes include: those due to *genetic defects of the  $\beta$ -cell*, including maturity-onset diabetes of the young (MODY), an autosomal dominant disease, and neonatal diabetes; those due to *diseases of the exocrine pancreas*, such as pancreatitis, post-pancreatectomy and pancreatic cancer; *endocrinopathies*, such as in Cushing's disease, acromegaly and glucagonoma, and those due to *drugs*, such as steroids and drugs used after organ transplantation.

**Gestational diabetes mellitus (GDM)** arises during pregnancy when the body cannot produce enough insulin to meet the need of the pregnancy. However, GDM does not exclude the possibility that unrecognized glucose intolerance may have existed before or during the pregnancy. Persons with GDM may continue to be hyperglycaemic after delivery.



# Vascular complications of diabetes, the co-morbidities

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Diabetes mellitus is associated with long-term vascular complications, which are frequently grouped into microvascular and macrovascular diseases. Microvascular complications include neuropathy, nephropathy and retinopathy, while macrovascular complications include cardiovascular and cerebrovascular diseases. Distal peripheral neuropathy and other vascular complications will be discussed briefly, mainly in relation to diabetic foot ulcers (DFU).

## **Microvascular complications**

### *Diabetic peripheral neuropathy (DPN)*

Distal symmetric polyneuropathy (DPN) is a devastating complication of diabetes mellitus. It affects up to 50% of patients with diabetes.<sup>7</sup> Based on an estimated diabetes prevalence of 592 million by the year 2035,<sup>6</sup> DPN may affect as many as 296 million people worldwide. DPN is the most common neuropathic complication in patients with diabetes. It is defined as “symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and microvascular alterations as a result of chronic hyperglycaemia exposure and cardiovascular risk factors. An abnormality of nerve conduction tests, which is frequently subclinical, appears to be the first objective quantitative indication of the condition”.<sup>8</sup> DPN is characterized by sensory loss, paraesthesia, and pain. Painful DPN affects almost 26% of diabetic patients.<sup>9</sup> Glycaemic control measures, such as HbA1c levels, diabetes duration and age, are considered major risk factors for DPN.<sup>10, 11</sup> Furthermore, hypertension, hyperlipidaemia, being overweight, and smoking are additional risk factors for the development of DPN.<sup>12</sup>

DPN is a major risk factor for foot ulcerations with an annual risk that is 5–7 times higher than in those without neuropathy.<sup>13</sup> In addition to the loss of pain, sensory neuropathy is associated with a loss of pressure awareness, temperature sensation and proprioception. Motor neuropathy, affecting both the intrinsic foot muscles and leg muscles, alters the biomechanics and, gradually, the foot anatomy due to postural instability and disturbed coordination caused by the lack of proprioceptive feedback from the lower extremities.<sup>14</sup> Foot deformities, limited joint mobility and altered loading of the foot are obvious consequences from these disarrangements. Furthermore, the presence of DPN may affect the clinical presentation of peripheral arterial disease (PAD) in patients with diabetes because patients with sensory loss may not experience the symptoms of claudication or the typical rest pain.<sup>15</sup>

Diabetic autonomic neuropathy in a lower extremity may contribute to the risk of foot ulceration by causing skin dryness and fissuring.<sup>16</sup> It can also cause arteriovenous shunting, resulting in a vasodilatory condition in the small arteries.<sup>17</sup>

### *Diabetic nephropathy (DN)*

DN is the leading cause of end-stage renal disease (ESRD), requiring dialysis and/or renal transplantation.<sup>18</sup> It occurs in 20–40% of patients with diabetes.<sup>19</sup> There is a stepwise progression in DN, from a hyperfiltration reversible phase to overt nephropathy with persistent albuminuria, followed by progressive deterioration of the glomerular filtration rate (GFR). Persistent albuminuria is considered to be the principal marker of kidney damage before the deterioration of the GFR.<sup>20</sup> Normal albumin urinary excretion is defined as <30 mg/24 h. In the early stage of DN, there is a persistent albuminuria in the range of 30–299 mg/24 h. Patients may progress to persistent albuminuria,  $\geq 300$  mg/24 h,<sup>19</sup> and these patients are more likely to progress to ESRD.<sup>21</sup> In clinical practice, measurement of the albumin-to-creatinine ratio (ACR) in a random spot collection is used instead, as it is less burdensome.<sup>19</sup> Normal values for ACR are 2.5 mg/mmol in males and 3.5 mg/mmol in females.<sup>22</sup> The national kidney foundation in the United States classifies chronic kidney disease mainly on the basis of the GFR (Table 1).<sup>20</sup>

**Table 1.** Stages of chronic kidney disease (adapted from Levey AS et al.<sup>20</sup>).

Stage	Description	GFR ( ml/min/1.73m2)
1	Kidney damage* with normal or increased GFR	$\geq 90$
2	Kidney damage* with mildly decreased GFR	60–89
3	Moderately decreased GFR	30–59
4	Severely decreased GFR	15–29
5	Kidney failure	<15 or dialysis

\*Kidney damage = any pathologic urine, blood, or imaging test for such damage.

The GFR is commonly estimated (eGFR) using serum creatinine, which can automatically be calculated in hospitals and reported for every serum creatinine measurement in adults.

Poor glycaemic control, hypertension and elevated plasma cholesterol are the major risk factors for the development and progression of DN,<sup>21, 23</sup> with age,<sup>21</sup> male sex<sup>21</sup> and smoking<sup>24</sup> as additional risk factors. DN, including both persistent albuminuria and a low GFR, has been shown to increase the risk for cardiovascular events and death.<sup>25-27</sup> DN with a GFR <60ml/min is associated with 46% higher mortality in patients with diabetes compared with those with diabetes but no DN. Mortality is substantially higher in patients on dialysis.<sup>28</sup>

Tight control of plasma glucose and blood pressure has been shown to reduce significantly the incidence and progression of DN.<sup>29-31</sup>

Furthermore, inhibition of the rennin-angiotensin-aldosterone system using an ACE inhibitor or an ARB has also been shown to reduce the progression of albuminuria,<sup>32</sup> and to slow the development of ESRD.<sup>33</sup>

Patients with DN have a worse prognosis regarding outcomes of foot ulcers. Renal failure in patients with diabetes has been shown to predict non-healing of both neuropathic and ischaemic foot ulcers.<sup>34, 35</sup> ESRD seems to have a stronger negative effect in patients with PAD than in those without PAD.<sup>35</sup>

Risk of amputation has also been found to be significantly higher in patients with diabetes and ESRD compared with those without ESRD.<sup>28, 36</sup> In a large systematic review on revascularization in patients with diabetes and ischemic foot ulcers, patients with ESRD had a 1-year limb salvage of 70% compared with all patients included in the review, who had 1-year limb salvage incidences of 85% after open surgery and 78% after endovascular revascularization. They also had a higher 30-day mortality of 4.6% compared with 1.4%, and poorer long-term outcomes with a 5-year mortality incidence of 91% compared with 46.5% of non-ESRD patients.<sup>37</sup>

### *Diabetic retinopathy (DR)*

DR is the most frequent cause of new cases of blindness among adults under the age of 75 year.<sup>19</sup> DR is commonly classified as non-proliferative background retinopathy (NPDR) and proliferative retinopathy (PDR). The latter is characterized by neovascularization, which is proliferation of new fragile vessels that haemorrhage easily. Diabetic maculopathy occurs when the macula is affected and central visual acuity is threatened. In this area of the retina, excessive vasopermeability and oedematous damage is referred to as diabetic macular oedema (DMO), which is the most common cause of blindness in diabetes.<sup>38</sup> DMO can occur at any stage of retinopathy, although it is most prevalent during the later phases of the disease. Visual impairment due to DR has a significant impact on a patient's quality of life.<sup>39</sup>

Almost all patients with type 1 diabetes of  $\geq 15$  years duration will have DR. In patients with type 2 diabetes and a duration  $\geq 15$  years, 85% of those receiving insulin treatment and 58% who did not receive insulin treatment will have DR.<sup>40</sup> In a 25-year follow up data of the same study, the cumulative incidence of any DR in patients with type 1 diabetes was 97%, while the cumulative incidence for DR progression was 83%.<sup>41</sup>

Factors that increase the risk of retinopathy include diabetes duration,<sup>40</sup> chronic hyperglycaemia,<sup>42</sup> nephropathy<sup>43</sup> and hypertension.<sup>44</sup> The male gender, hyperglycaemia and BMI have been shown to be associated with the progression of DR.<sup>41</sup> Intensive glycaemic control has been shown to delay the onset and slow the progression of DR, both in type 1<sup>45</sup> and type 2 diabetes.<sup>46</sup>

Patients with poor vision from advanced DR had a higher risk of foot ulcer development.<sup>47</sup> In a Danish study of newly diagnosed type 2 DM patients followed up for 19 years, DR at diagnosis was shown to be associated with a higher incidence of foot ulcer.<sup>48</sup> In the same study, both DR and impaired vision at diagnosis were independent predictors for later amputations. Similar results were reported in The Wisconsin Epidemiologic Study of Diabetic Retinopathy, in which DR was shown to be associated with a higher incidence of diabetes related amputations. PDR had a clearly higher incidence compared with NPDR.<sup>49</sup>

## **Macrovascular complications**

### *Cardiovascular disease (CVD)*

CVD is the major cause of morbidity and mortality for individuals with diabetes.<sup>19</sup> In the United States; adults with diabetes have heart disease death rates about 2 times higher than adults without diabetes.<sup>50</sup>

The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that there was no statistically significant risk reduction of myocardial infarction in intensively treated patients with type 2 diabetes compared to those who had conventional treatment. However, at a 10-year post-trial monitoring, the UKPDS follow-up data demonstrated a persistent 15% risk reduction of myocardial infarction ( $P = 0.01$ ) following intensive treatment.<sup>51</sup> Similarly, in patients with type 1 diabetes, intensive treatment reduced the risk for any CVD by 42%, and the risk of non-fatal myocardial infarction, stroke and death from CVD was reduced by 57%.<sup>52, 53</sup>

Patients with diabetes and foot ulcers have higher prevalence of cardiovascular morbidity, both coronary artery disease and cerebrovascular disease, as well as a higher incidence of new onset vascular events at 5-years follow-up compared with patients without foot ulcers.<sup>54</sup> Furthermore, a low ankle-brachial index (ABI) has been shown to predict fatal and non-fatal cardiovascular events.<sup>55, 56</sup>

### *Cerebrovascular disease*

The risk for cerebrovascular disease is 2 times higher among people with diabetes than among individuals without diabetes.<sup>50</sup> At the 10-year post-trial follow-up of UKPDS, 6% of patients with type 2 diabetes had cerebrovascular disease.<sup>57</sup> Both previous and new onset cerebrovascular diseases were more common among patients with diabetes and foot ulcers than those without foot ulcers.<sup>58</sup>

Patients who lacked the capacity to walk due to cerebrovascular disease have been generally excluded from revascularization, thus increasing the risk of amputation in case of non-healing.<sup>59</sup> In fact, the lack of walking capacity has been shown to predict non-healing of ischaemic foot ulcers in patients with diabetes.<sup>35</sup>

## The diabetic foot ulcer (DFU)

---

The diabetic foot is defined as an infection, ulceration or destruction of deep tissues of the foot, associated with neuropathy and/or PAD in the lower extremity of people with diabetes.<sup>1</sup> DFU is a major complication of diabetes. The prevalence of foot ulcers among diabetic patients is estimated to be 4–10%, with a life time risk as high as 25%.<sup>60</sup> DFUs are associated with an increased risk of lower limb amputation, and, thus, the primary aim of treatment is limb preservation.<sup>1</sup> Of all amputations in patients with diabetes, almost 85% are preceded by a foot ulcer that subsequently progresses to a severe infection or gangrene.<sup>61</sup> DFUs are associated with a lower quality of life, which affects both physical and mental health. Moreover, they are also associated with a substantial economic burden, in which hospitalization and amputation are responsible for 50% of the costs.<sup>62</sup>

### Aetiology

The development of DFUs is attributed to many interacting factors, most commonly peripheral neuropathy and PAD. Thus, DFUs are usually classified as neuropathic, neuroischaemic or ischaemic ulcers (Photo). The prevalence of neuroischaemic and ischaemic ulcers has been rising since the 1990s, from approximately one-third of patients,<sup>63, 64</sup> to become probably the most common aetiology of DFUs.<sup>34, 35, 65</sup> This is probably due to the increased awareness of the role of ischaemia in DFUs and their adverse outcomes, although it may be due to improved diagnostic methods, which has implications for guidelines for diagnostic criteria.<sup>64</sup>

Other factors that can contribute to DFU development include foot deformities, trauma, visual impairments, previous amputations, and previous foot ulcerations.<sup>66-68</sup> The triad of neuropathy, trauma and deformity has been described previously as the most frequent cause of DFUs.<sup>68</sup> Ill-fitting shoes are a common cause of trauma in patients with diabetes and DPN. Neuro-osteoarthropathy, a devastating complication of the foot in patients with diabetes, may lead to significant deformities of the foot.<sup>1</sup>

Infection is seldom the direct cause of an ulcer. However, once an ulcer is complicated by an infection, the risk for subsequent amputation is grossly increased, particularly in the case of ischaemic and neuroischaemic ulcers.<sup>1</sup> The combination of infection and PAD in patients with DFU indicates a worse prognosis.<sup>35, 69</sup> Foot infections are now the most frequent diabetic complication requiring hospitalization and the most common precipitating event leading to lower extremity amputations. Infections commonly follow trauma. Deep DFUs

penetrating to bone, DFUs with durations > 30 days, a history of recurrent ulcers, DFUs of traumatic aetiology, and the presence of PAD have been related to an increased probability of the development of infections in patients with DFUs.<sup>70</sup>



A neuroischaemic foot ulcer in a patient with diabetes.

## Management

The basic strategy for the management of DFUs is based on prevention, including patient and healthcare provider education, and multi-disciplinary treatment of foot ulcers. The aim is to avoid amputation in these patients.<sup>1</sup> A 50% reduction in amputation was set and adopted as a goal by the European Declaration of St Vincent in 1989.<sup>71</sup> The reason for employing a strategy using a multi-disciplinary

team approach is due to the complexity of DFUs, which are a part of a multi-factorial disease with several concurrent factors acting together.

### *Prevention of DFUs*

The foot is considered at-risk when any of the following is present: neuropathy, PAD, deformity, loss of joint mobility, callus or present or previous ulcer/amputation.<sup>1</sup>

*Regular inspection* and examination of the at-risk foot every 1–6 months (Table 2) is an essential part of the preventive management of DFUs, as the absence of symptoms in patients with diabetes does not exclude foot problems. External trauma, frequently inappropriate footwear, is a common cause of DFUs, and, thus, inspection of the footwear should be included in the examination.

**Table 2.** Risk categorization of DFUs, IWGDF consensus.<sup>1</sup>

Category	Risk profile	Inspection frequency
1	no sensory neuropathy	once a year
2	sensory neuropathy	every 6 months
3	sensory neuropathy, signs of PAD and/or foot deformities	every 3 months
4	previous ulcer	every 1–3 months

*Education* of the health care providers, including physicians, will improve the early detection and care of DFUs, especially in high-risk patients. Education of the patients and family members will enhance their motivation and skill by teaching them how to recognize early foot problems.<sup>1</sup>

*Offloading* of the diabetic foot has an important role in the prevention and treatment of DFUs. Custom-modelled insoles and footwear fitting the foot form are used to reduce peak plantar pressure, thus preventing plantar ulceration. The total contact cast (TCC), used as a treatment, is the most effective offloading for patients with non-infected plantar ulcers. Removable walkers and half-shoes are other alternatives.<sup>72</sup>

### *Treatment of DFUs*

*The multi-disciplinary* team management of patients with DFUs has been suggested to be a cost-effective approach to reduce the overall cost of care.<sup>73</sup> It has also been shown to be associated with an improved healing rate, reduction in



amputation rate,<sup>74-76</sup> and a 50% reduction in ulcer recurrence.<sup>77, 78</sup> Health care organizations that offer effective communication and collaboration between health care providers at different levels, patient education, and well operating referral patterns that enable prompt referral to a diabetic foot care team are crucial for improving outcomes.<sup>1</sup> The management of DFUs includes strategies for the treatment of peripheral ischaemia, oedema, pain, infection, metabolic disturbances, malnutrition, off-loading, topical treatment, foot surgery aggressive management of inter-current disease, and a coordinated system for the support of both patients and staff to implement the treatment strategy. The multifactorial treatment of DFUs is summarized in Table 3.<sup>79</sup>

*Negative pressure wound therapy* (NPWT) is an example of a technology that has been shown to significantly improve wound conditions, reduce the time to wound closure, and reduce the incidence of minor amputations in patients with DFUs.<sup>80, 81</sup> NPWT is mainly used in post-operative wounds or DFUs with cavities and large cross-sectional areas.

*Treatment of infection* with antibiotics is necessary for all infected ulcers.<sup>79</sup> The initial antibiotic therapy is usually empirical. The selected antibiotic agent should be targeted at the likely pathogens, usually *Staphylococcus aureus* and aerobic streptococci. When culture and sensitivity results are available, a more specific antibiotic therapy is considered, taking into account the clinical response to the empirical treatment.<sup>1</sup> Most deep infections require surgical interventions, such as incisions and debridement. Further surgical corrections of deformities may be needed for the healing of ulcers and the prevention of their recurrence.<sup>82</sup>

## **Outcomes and survival**

The potential outcomes of DFUs are primary healing, healing after minor amputation, which represent minimal tissue loss, major amputation, or non-healing. Ulcer recurrences or new ulcerations and new amputations are measures of late complications or progression of the disease.<sup>83</sup> In large cohort studies of patients with DFUs, primary healing or healing without major amputation are the most frequently reported end points.<sup>34, 35</sup> However, studies on revascularization usually report limb salvage as an outcome.<sup>37</sup>

### *Factors related to outcomes*

There are multiple factors that have been shown to be related to the outcomes of DFUs. Diabetes, *per se*, was found to predict unfavourable outcomes after peripheral revascularization in patients with critical limb ischaemia (CLI), compared with those without diabetes.<sup>84-86</sup> PAD is considered to be the main factor affecting the outcomes of ischaemic / neuroischaemic DFUs.<sup>1</sup>

**Table 3.** Multifactorial management of DFUs (adapted from Apelqvist J et al.<sup>79</sup>).

<b>Goal</b>	<b>Investigation/evaluation</b>	<b>Treatment</b>
<b>Improve circulation</b>	Non-invasive vascular testing: ABI / TBI, TcPo <sub>2</sub> Duplex (ultrasound) Invasive vascular testing: Angiography MRA / CTA /CO <sub>2</sub> angiography	Percutaneous angiography (PTA) Subintimal angioplasty Reconstructive vascular surgery Vascular agents HBO
<b>Treat infection</b>	Superficial/deep infection, osteomyelitis ESR, CRP, white blood count, bacterial culture, bone biopsy, X-ray, CT-bone scan, MRI	Antibiotics oral/parenteral Incision/drainage, resection Amputation
<b>Remove oedema</b>	Evaluate the cause of oedema	External compression therapy Intermittent compression (pumps) Diuretics
<b>Pain control</b>	Cause/type of pain Pain evaluation protocol/diary Visual analogue scale	Analgesic agents Immobilisation/offloading
<b>Improve metabolic control</b>	HbA1c self-monitoring of glucose	Insulin treatment often necessary/nutritional support
<b>Offloading</b>	Type and site of wound biomechanical evaluation Mobility/walking capacity	Protective/therapeutic footwear Insoles/orthoses Total contact cast/walkers Crutches / wheelchair, bed rest
<b>Wound bed preparation</b>	Type, site, condition of the ulcer necrosis/debris exudation peri-wound maceration signs of inflammation granulation	Topical treatment/dressings Debridement Control of exudation, moist wound healing, control of infection NWPT Tissue engineering/growth factors, matrix modulation
<b>Removal of dead tissue</b>	Extent of tissue destruction Infection ischemia	Incision/resection/amputation
<b>Correction of foot deformities</b>	Evaluation of foot deformities	Corrective foot surgery
<b>Improve general condition</b>	Dehydration / malnutrition Intercurrent disease Congestive heart failure, nephropathy Metabolic syndrome Smoking habits History of abuse	Fluid and nutrition replacement therapy Aggressive treatment of intercurrent disease Antiplatelet drugs, antihypertensive agents, lipid decreasing agents Cessation of smoking, physiotherapy

In the Eurodial study, a European multi-centre study of 1,088 patients with DFUs, 48% had PAD.<sup>35</sup> PAD was a strong predictor of non-healing. Similar results were seen in a Swedish study that included 2,511 patients with DFUs.<sup>34</sup>

Infection is also an important factor that affects outcomes.<sup>35</sup> The combination of infection and PAD is a major risk factor for amputation.<sup>35, 69</sup> Conversely, the early diagnosis of PAD, with the extensive use of revascularization and aggressive treatment of infection, has been shown to improve DFU outcomes.<sup>87</sup> The presence of co-morbidities, such as cardiovascular disease,<sup>34, 88</sup> end-stage renal disease<sup>34, 36</sup> and severe retinopathy,<sup>49</sup> have been shown to be related to outcome. The extent of tissue involvement<sup>34, 35, 87, 89</sup> and peripheral oedema have also been associated with worse healing in patients with DFUs.<sup>34, 35</sup>

Ulcer location is related to outcome, as the time to ulcer healing increases progressively from the toe to the mid-foot to the heel.<sup>90</sup>

Other factors such as male gender,<sup>49, 91</sup> age,<sup>92</sup> metabolic control as measured by HbA1c,<sup>49, 91</sup> diabetes duration,<sup>34, 91</sup> and socio-economic status<sup>91, 92</sup> have also been reported to affect outcomes in patients with DFUs.

Health care organizations that offer effective communication and collaboration between health care providers at different levels, patient education, and well operating referral patterns that enable prompt referrals to a diabetic foot care team are crucial for improving outcomes.<sup>1</sup>

### *Outcomes*

It is difficult to obtain reliable data on DFU healing, or to compare outcome between studies, due to several confounding factors that influence outcomes, including different outcome reporting, inclusion criteria, observation times, prevalence of neuropathic vs. ischaemic/neuroischaemic ulcers, prevalence of diabetes among patients included, source of the population included, whether from out-patient clinics, in-hospital patients or population-based, reporting of co-morbidities, and treatment strategies.

Margolis DJ et al. reported the outcomes of neuropathic foot ulcers in >31,000 patients with diabetes in a retrospective study using a patient record database of the Curative Health Services. Fifty percent of the ulcers healed at 20 weeks following standard therapy.<sup>93</sup> However, it should be noted that the follow-up time was relatively short. In another study of 194 patients with DFUs, most (67%) were neuropathic ulcers. Sixty-five percent of patients healed without amputation after a minimum follow-up of 6 months. The median healing time was 10 weeks (8.4–11.6).<sup>89</sup>

In the Eurodial study, a multi-centre prospective study of 1,088 patients with DFUs in Europe, at 1 year, 77% of patients healed primarily or after minor

amputation, 12% were unhealed, 5% had a major amputation, and 6% died unhealed.<sup>35</sup> Almost 48% of the patients had PAD.

In a large Swedish study of 2,511 patients with DFUs presenting at a diabetic foot clinic, 65% healed primarily, 9% after minor amputation and 8% after major amputation, while 17% died unhealed. The median healing time was 18 (1–235) weeks and almost 50% of the patients had PAD.<sup>34</sup>

In a systematic review of the effectiveness of revascularization in patients with DFUs and PAD, the overall healing rate at 1-year follow-up in seven studies (the numbers of patients with diabetes included in these studies ranged from 33–993) that reported ulcer healing as an outcome following revascularization was 60% or more.<sup>37</sup>

Larsson J et al. have previously shown, in a Swedish study, a substantial decrease in the incidence of major amputations among patients with DFUs that were examined between the years 1982 and 2001.<sup>94</sup>

There is very limited information regarding ulcer outcome among patients with severe PAD, but without revascularization. Lepántalo M et al. studied 105 patients (136 legs) with CLI, 50% had diabetes. At 1-year follow-up, 54% of legs were saved from amputation.<sup>95</sup> In a similar study, Marston WA et al. examined 142 patients with severe PAD who were not treated with revascularization. Seventy percent of the patients had diabetes. At 1-year follow-up, 52% healed primarily and 23% had an amputation.<sup>96</sup>

#### *Long-term outcomes and survival*

DFUs are considered a lifelong condition because patients with previous ulcers are always at high risk of developing a new ulcer and re-amputation.<sup>97-100</sup> In a long-term follow-up of patients (n=468) with diabetes, healed with or without amputation from previous foot ulcer, 34%, 61% and 70% of the patients had developed a new foot ulcer after 1, 3 and 5 years of observation respectively.<sup>97</sup>

Patients with DFUs have a higher risk of death compared with those without diabetes.<sup>101</sup> In the previously mentioned systematic review of the effectiveness of revascularization in patients with DFUs and PAD, median mortality at 1 year following revascularization was 13.5%, while it was 46.5% at 5 years.<sup>37</sup> Patients with diabetes and CLI not available for revascularization had 1 year survival of 46%.<sup>95</sup> Mortality is substantially higher in patients with ESRD.<sup>28</sup> The most common cause of mortality in patients with diabetes and foot ulcers is cardiovascular disease.<sup>98, 102</sup> However, survival in patients with DFUs seems to have improved over the past decades.<sup>103</sup>

# Peripheral arterial disease of lower extremities (PAD) in patients with diabetes

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## Epidemiology

PAD is a progressive arterial occlusion located in lower extremities that is caused by atherosclerosis, with or without symptoms in the leg or foot.<sup>104</sup> PAD is a sign of generalized atherosclerosis, and is associated with a higher risk of cardiovascular mortality, coronary heart disease and stroke.<sup>55, 105</sup> In a large systematic review of the literature on the prevalence of PAD, one in ten people aged 70 years and one in six people older than 80 years had PAD.<sup>106</sup> In a recently published large population study in which >3.6 million participants were screened for cardiovascular disease, the prevalence of PAD was significantly increased in patients with diabetes compared to those without diabetes.<sup>107</sup> Patients with diabetes have been shown to have a four-fold higher risk for PAD.<sup>108</sup> In the United Kingdom Prospective Diabetes Study, 11% of patients with type 2 diabetes had PAD six years after diagnosis, and for each percent increase in HbA1c the relative risk for PAD increased by 28%.<sup>109</sup> PAD was found in 50% of patients with DFUs,<sup>34, 35, 110</sup> and is considered to be a major risk factor for major amputations.<sup>92, 111</sup>

*PAD in diabetes* shows a different nature. Patients with diabetes more commonly have infra-popliteal occlusive arterial disease,<sup>112, 113</sup> which is more severe in its extent, with a high prevalence of long occlusions, and poor outcomes compared with patients without diabetes.<sup>113, 114</sup> Collateral arterial formation has been shown to be impaired in patients with diabetes.<sup>115</sup> Furthermore, PAD in patients with diabetes is more frequently associated with media sclerosis (Monckeberg's sclerosis), especially in patients with neuropathy.<sup>116</sup> Media sclerosis is characterized by calcification of the smooth muscle cells in the arteries. It can cause incompressible arteries and falsely elevated blood pressure especially at the ankle level, or a normal ankle index despite clinically significant PAD.<sup>59</sup> Toes are significantly less affected by media sclerosis,<sup>116</sup> thus, measuring toe blood pressure may be better for evaluating the arterial circulation of the legs in patients with media sclerosis. Media sclerosis has been found to be associated with an increased risk of amputation, nephropathy, retinopathy, coronary artery disease and all-cause mortality.<sup>117</sup>

Diabetes is associated with impaired microcirculation. There is reduced capillary blood flow that is attributed to an arterio-venous shunting, bypassing the nutritional skin capillaries.<sup>118</sup> An obvious structural change in patients with

diabetes and microangiopathy is the thickening of the capillary basement membrane. This may impair normal transport across capillary walls. Furthermore, the elastic properties of the capillary walls are also reduced, limiting their capacity for vasodilation and, hence, impairing the normal hyperaemic response to injury.<sup>119</sup>

## **Risk factors for the development of PAD**

Various modifiable and non-modifiable factors have been associated with an increased risk of developing PAD.

*Smoking* is to be considered the most important modifiable risk factor. The association between smoking and PAD is probably stronger than that between smoking and coronary artery disease.<sup>120</sup> The risk of PAD conferred by smoking is dose-dependent.<sup>121</sup> Heavy smokers had a four-fold higher risk for symptomatic PAD than non-smokers,<sup>120, 122</sup> whereas the relative risk for intermittent claudication (IC) was 3.7 in smokers compared with 3.0 in ex-smokers.<sup>123</sup> Smoking in patients with diabetes was associated with more amputations as well as more proximal amputations, compared with those who did not smoke.<sup>124</sup>

*Diabetes* is a strong risk factor for the development of PAD.<sup>108</sup> IC is two times more common in patients with diabetes than without diabetes.<sup>125</sup> In a meta-analysis of observational studies, each 1% increase in HbA1c was associated with a 28% increased risk of PAD in patients with type 2 diabetes, and a 32% increased risk in patients with type 1 diabetes.<sup>126</sup> The risk of PAD is 40–50% higher in individuals with pre-diabetes.<sup>127</sup> PAD in patients with diabetes is more aggressive, with a risk of major amputation 5–10 times higher than for patients without diabetes.<sup>120, 125</sup> Diabetes duration has also been shown to be a risk factor for PAD.<sup>109, 128, 129</sup>

*Hyperlipidaemia* is also associated with an increased risk of PAD. Elevated serum total cholesterol >7 mmol/L has been shown to be associated with a two-fold increase in the incidence of IC.<sup>120</sup> Serum triglycerides have been shown to be associated with progression of PAD and onset of critical ischaemia.<sup>130</sup>

*Hypertension* is associated with an increased risk of PAD.<sup>109, 122, 131</sup> In the Framingham study, hypertension, a systolic blood pressure >140 mmHg or a diastolic blood pressure >90 mmHg, was associated with increased risk of IC.<sup>132</sup> Increased systolic blood pressure has been shown to be an independent risk factor for PAD in patients with type 2 diabetes. Each 10 mmHg increase in systolic blood pressure was associated with a 25% increased risk of PAD.<sup>109</sup>

The risk of PAD, as stated earlier, increases with *age*.<sup>106, 128, 131</sup> In the Framingham study, males exhibited a two-fold greater incidence of IC at all ages.<sup>132</sup> Jensen SA et al. studied the prevalence of IC in 20,000 individuals between 40–69 years of

age, and found no difference between males and females.<sup>133</sup> The Genetic Epidemiology Network of Arteriopathy (GENOA) study showed that *African-Americans* have a higher risk of PAD compared with non-Hispanic whites even after adjusting for several other risk factors.<sup>134</sup> A higher *CRP* level, an inflammatory marker, has been described as independent predictor of PAD.<sup>135</sup> Similarly, a higher fibrinogen level was shown to be associated with a higher risk of PAD.<sup>131, 136</sup> *Hyperhomocysteinemia* has also been reported to be higher in individuals with vascular disease, especially young patients.<sup>120</sup>

## Clinical presentation

Many patients with diabetes and PAD are *asymptomatic* due to decreased pain perception, presumed to be a result of neuropathy, which may delay the presentation to health care providers and, thus, treatment. Many patients with diabetes and PAD are asymptomatic due to a low degree of activities, such as a lack of walking capacity. A lack of symptoms may lead to late presentation with foot ulcer or gangrene, indicating severe PAD with a threat of major amputation. In a Swedish population-based study (n=5,080) of patients 60–90 years of age, 62% of those with PAD were asymptomatic. Seventeen percent of individuals with PAD had diabetes compared with 9% of those without PAD.<sup>137</sup>

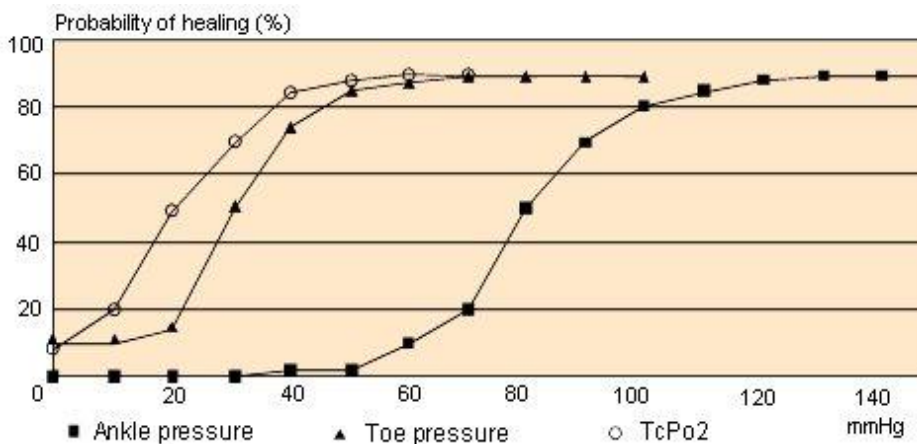
*IC* is the most frequent symptom. It is characterized by pain or cramps when walking which resolves after rest. *IC* is most commonly observed in the leg, but can occur in the buttock, thigh, or foot, depending on the location of arterial lesion. Studies have shown that 11–38% of patients with PAD suffer from *IC*.<sup>137-139</sup> In the Framingham study, patients with diabetes and PAD were 2-3 times more likely to develop *IC* compared with those without diabetes.<sup>132</sup> However, in patients with diabetes and PAD, less than 25% reported *IC*, which may delay the diagnosis of ischaemia.<sup>1</sup>

*Rest pain* in the foot, often at night, which is temporarily improved by lowering the foot or walking, indicates *CLI*. Rest pain occurs most commonly when ankle pressure is <50 mmHg or toe pressure is <30 mmHg.<sup>120</sup> *CLI* is a limb-threatening condition, defined as patients with typical chronic ischaemic rest pain or patients with ischaemic skin lesions, either ulcers or gangrene attributed to objectively proven PAD.<sup>120</sup> Gangrene is the ultimate sign of irreversible tissue destruction. Indeed, in individuals with diabetes, 30–50% of their foot ulcers already have gangrene and, therefore, these patients often are not considered candidates for revascularization.<sup>1, 74</sup> In *CLI*, progress to gangrene occurs in 40% of patients with diabetes compared with 9% in those without diabetes.<sup>140</sup>

## Diagnosis and severity of PAD

The International Working Group on the Diabetic Foot (IWGDF) regularly publishes consensus guidelines for the management and prevention of the diabetic foot; these guidelines were last updated in 2011.<sup>1</sup> These guidelines suggest, in addition to a thorough history taking for symptoms of PAD and palpation of pulses in the lower limb (including posterior tibial and dorsalis pedis arteries), a hand-held Doppler evaluation of the flow signals from both foot arteries, and a measurement of the ankle brachial index (ABI) should be included in the evaluation of patients with DFUs. In case of diagnostic uncertainty, measurement of the toe brachial index (TBI) or transcutaneous pressure of oxygen (TcPO<sub>2</sub>) may provide additional diagnostic value.<sup>141</sup> PAD is likely when the patient has claudication or rest pain, both foot pulses are absent at palpation, or absent or monophasic Doppler signals are obtained from one or both foot arteries. An ABI < 0.9, or a TBI < 0.7 are signs of PAD. As ankle pressure might be falsely elevated because of calcification of the arteries it is preferred to use toe pressure or TcPO<sub>2</sub> in addition.

The probability of ulcer healing, based on perfusion testing using absolute values, follows a sigmoid curve (Figure 1).<sup>142</sup> An ABI < 0.6 indicates severe ischaemia with significant impairment of healing probability<sup>1</sup>. An ABI > 0.6 has less predictive value and in these patients, toe pressure and/or TcPO<sub>2</sub> should be measured.



**Figure 1.** Schematic estimate of the probability of the healing of foot ulcers and minor amputations in relation to ankle blood pressure, toe blood pressure and TcPO<sub>2</sub> based on selected reports.<sup>142</sup>



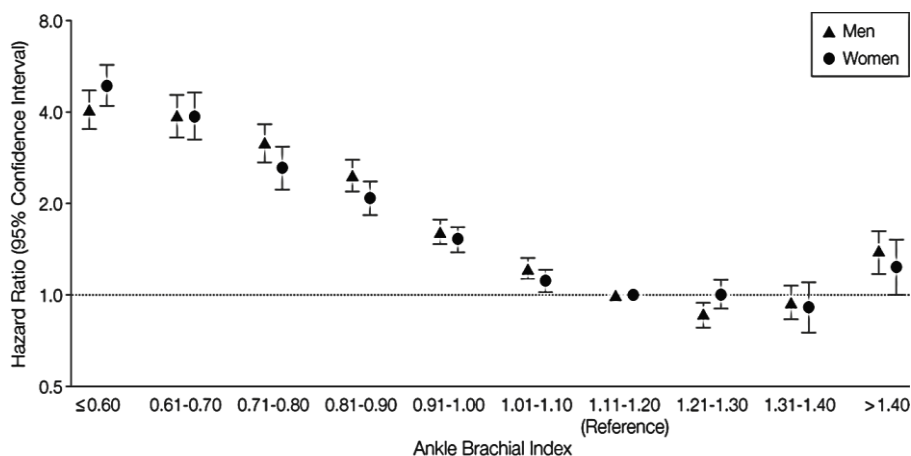
The probability of foot ulcer healing in patients with diabetes is high when toe pressure is >55 mmHg and the TcPO<sub>2</sub> is >50 mmHg. Healing is usually severely impaired when toe pressure is <30 mmHg and TcPO<sub>2</sub> is <30 mmHg.

## Investigation of PAD

There are non-invasive tests to diagnose and evaluate the severity of PAD, such as ankle blood pressure, ABI, toe blood pressure, TBI and TcPO<sub>2</sub>, and arterial imaging examinations, such as duplex ultrasound imaging (DUS), computed tomography angiography (CTA), magnetic resonance angiography (MRA) and digital subtraction angiography (DSA).

*Ankle blood pressure and ABI* are the most commonly used diagnostic tests for PAD. They are inexpensive and simple non-invasive tests. ABI is considered as non-compressible at values defined as >1.31. Normal values are 0.91 to 1.31, and the cut-off point for diagnosis of PAD is  $\leq 0.9$ .<sup>143</sup> Using an ABI  $\leq 0.9$  to diagnose PAD is almost certain, with 95% sensitivity and 100% specificity, compared with angiography.<sup>120</sup>

A low ABI has been shown to predict mortality (Figure 2) and cardiovascular events, and can be used as a marker of general atherosclerosis. In a meta-analysis by Fowkes FG et al., an ABI  $\leq 0.9$  was associated with a doubling of 10-year total mortality, cardiovascular mortality, major coronary events<sup>144</sup> and strokes.<sup>55</sup>



**Figure 2.** Hazard ratios for total mortality in men and women by ABI.<sup>144</sup>

ABI is not accurate in the presence of non-compressible arteries due to media sclerosis causing false negative values, especially in elderly patients or patients with diabetes and/or renal failure. ABI provides information on the arterial circulation in the lower limb, although cannot localize the anatomical lesion.<sup>145</sup>

*Toe blood pressure and TBI* are commonly used, as toes are significantly less affected by media sclerosis,<sup>116</sup> and are recommended for the evaluation of foot circulation, especially at false high ABIs, but even when the ABI is above 0.6 or the ankle pressure is >70 mmHg, in which their healing predictability is poor.<sup>59</sup> A TBI <0.7 strongly suggests PAD. However, measuring toe blood pressure is more challenging technically compared with ankle blood pressure, and it can be impossible to measure in the presence of tissue loss.

*TcPO2* is a measure of partial pressure of O<sub>2</sub> at the skin surface using heated electrodes. Normally TcPO<sub>2</sub> is >50 mmHg, while values <40 mmHg predict impaired healing.<sup>146</sup> In CLI, TcPO<sub>2</sub> is almost always <30 mmHg, and usually <20 mmHg. TcPO<sub>2</sub> has a wound healing predictive accuracy of 83%.<sup>147</sup> TcPO<sub>2</sub> predicts healing after lower limb amputation. In a systematic review by Arsenault KA et al., patients with TcPO<sub>2</sub> values <40 mmHg had a 24% increased risk of healing complications after lower limb amputations compared with a 41% increased risk at values <30 mmHg, a 75% risk at values <20 mmHg, and an 80% risk at values <10 mmHg.<sup>148</sup> TcPO<sub>2</sub> is not affected by media sclerosis, and, thus, can be used to evaluate foot circulation in these cases. However, use of TcPO<sub>2</sub> has its limitations. TcPO<sub>2</sub> cannot be used in oedematous skin,<sup>149</sup> plantar skin, callus, or bone or cellulitis, which are likely to give false values. TcPO<sub>2</sub> is also time consuming.

*Arterial imaging.* DUS is a non-invasive method, well tolerated by patients, and has no side effects. However, DUS is highly operator-dependent. Moreover, its accuracy in visualising aorto-iliac arteries, distal arteries and collaterals is limited.<sup>145</sup> In a systematic review, DUS was found to have a sensitivity of 88% and a specificity of 96% when detecting a  $\geq 50\%$  stenosis compared with DSA.<sup>150</sup> In the same study, MRA had the highest diagnostic accuracy with a sensitivity of 95% and a specificity of 97%, while CTA had a sensitivity of 91% and a specificity of 91%. In another systematic review, CTA had a pooled sensitivity of 95% and a pooled specificity of 96% when detecting a >50% stenosis or occlusion compared with DSA.<sup>151</sup> Both CTA and MRA are commonly used to visualize the arterial lesions in lower limbs. However, MRA has a higher diagnostic accuracy in peripheral arteries compared to CTA, and unlike DUS and CTA, MRA is unaffected by arterial calcification.<sup>145</sup>

DSA is a diagnostic imaging test that provides a complete arterial map of lower limb circulation that is easily interpretable, and it is still the only universally accepted method for guiding percutaneous endovascular procedures.<sup>145</sup>

## Non-invasive intervention of PAD

The rates of diabetes-related complications, including amputations<sup>152</sup> and survival of patients with diabetic foot ulcers<sup>103</sup> have declined during the last two decades. This is probably, in part, due to improved managements of cardiovascular risk factors and glycaemic control. The medical treatment of PAD mainly improves the cardiovascular outcomes. There are currently no convincing data showing a delay or reduction of the progression of PAD by antiplatelet therapy. A summary of the non-invasive treatment of PAD in patients with DFUs is given in Table 4.<sup>153, 154</sup>

*Intensive glycaemic control* in patients with type 1 diabetes has been shown to reduce the risk of cardiovascular disease outcomes by 42%, and of PAD by 22%.<sup>53</sup> This risk reduction for PAD could not be shown in patients with type 2 diabetes who received intensive anti-diabetic treatment compared to those who had conventional therapy.<sup>51, 158</sup> However, in a recent Cochrane review, intensive glucose treatment in patients with type 2 diabetes was associated with a reduced risk of lower extremity amputations.<sup>159</sup> Similarly, a recent study has shown that improved glycaemic control in patients with type 1 diabetes is associated with improved skin microcirculation and with a lower incidence of ischaemic foot ulcers.<sup>160</sup>

*Antiplatelet therapy.* In a meta-analysis of the effect of anti-platelet therapy on vascular events, there was a 22% reduction in severe vascular events, with a 22% risk reduction of ischaemic events for patients with PAD. Aspirin, 75–150 mg daily, was an effective dose during the long term.<sup>161</sup> Low doses of aspirin (75–325 mg) are as effective as higher doses, while higher doses were associated with an increased risk of bleeding, whereas very low-doses (<75 mg) were less effective.<sup>162</sup> In the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) trial, there were significantly lower risks of myocardial infarctions, strokes, and death from vascular causes in patients treated with Clopidogrel, 75 mg/day, compared with aspirin, 325 mg/day. The effect was more pronounced in patients with PAD.<sup>163</sup>

*Lipid-lowering treatment* should be added to lifestyle therapy irrespective of baseline lipid levels in patients with diabetes and cardiovascular disease, or in those over 40 years of age and at least one cardiovascular risk factor.<sup>19</sup> In a Cochrane review of 18 RCTs with 10,049 patients on the effect of lipid-lowering treatment in patients with PAD, lipid-lowering treatment reduced the number of cardiovascular events and improved both total and pain-free walking distances.<sup>164</sup>

**Table 4.** Non-invasive treatment of PAD in patients with DFUs.

Category	Treatment	Remarks
<b>Smoking cessation</b>	-Use of tobacco should be stopped -Patients may be offered behavioural and pharmacological treatment	Active smoking has also been shown recently to increase risk of early graft failure after infra-inguinal bypass surgery <sup>155</sup>
<b>Glycaemic control</b>	Anti-diabetic therapy to lower HbA1c to target level	Reduce microvascular complications, and potentially reduce amputation
<b>Antiplatelet drugs</b>	-Aspirin, 75–325 mg daily, is recommended. -Clopidogrel, 75 mg daily, is a safe and effective alternative to aspirin	In the absence of specific indications, treatment with Warfarin is of no benefit
<b>Lipid lowering drugs</b>	Use of statin to lower LDL-cholesterol to <2.6 mmol/L	Targeting LDL-cholesterol <1.8 mmol/L can be used in patients with a high risk of ischemic events
<b>Blood pressure (BP) control</b>	BP <130/80 mmHg is the target in patients with diabetes. ACE inhibitors are reasonable in patients with diabetes	-Beta-blockers are not contra-indicated -Ramipril in patients with IC has been shown to increase pain-free and maximum treadmill walking times compared to a placebo. <sup>156</sup>
<b>Other therapies</b>	-Iloprost: is used mostly in patients with CLI but is not available for invasive vascular intervention - Gene therapy: angiogenic growth factors involving vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF)	-It may improve rest pain and ulcer healing in patients with CLI. <sup>157</sup>  - interesting and promising therapies that stimulate the development of collaterals <sup>154</sup>

*Hyperbaric oxygen therapy (HBO)* has been suggested as an adjunctive therapy in patients with diabetes and chronic ischaemic foot ulcers not responding to optimal treatment with a multi-disciplinary approach, especially those not available for revascularization. It is a treatment designed to increase the supply of oxygen to wounds. In a recent retrospective study including 6,259 patients with non-ischemic DFUs, HBO did not improve the healing probability or prevent amputation.<sup>165</sup> Two randomized controlled studies, by Abidia A et al. and Löndahl M et al.,

which included patients with PAD, reported significant improvements in the long-term healing rates of foot ulcers.<sup>166, 167</sup> In a systematic review of randomized controlled studies on HBO, HBO was found to improve ulcer healing in the short term but not in the long term. No significant differences were seen in the major amputation rate.<sup>168</sup> A more recent systematic review of studies on the effect of HBO on DFU healing concludes that HBO improves ischaemic foot ulcer healing in patients with diabetes, in the long term, without consistent evidence for HBO preventing major amputation.<sup>169</sup> However, the number of patients included in these studies was small and larger trials are needed to draw definite conclusions.

## **Invasive revascularization in PAD**

Invasive revascularization has been indicated in CLI, irrespective of the size of DFUs. The goals of revascularization in these patients have been pain-control, ulcer healing and avoidance of amputation.<sup>120</sup> In patients with CLI not available for revascularization or with failed revascularization attempts, approximately 40% will undergo amputation and 20% will die within six months.<sup>120</sup> Most publications on revascularization have been case series or cohort studies, in which outcomes are reported after a specific intervention.<sup>101, 170-172</sup> Thus, recommendations are based on a low level of evidence.<sup>173</sup> Furthermore, many studies considering revascularization for CLI include both patients with and without diabetes,<sup>37, 101, 174, 175</sup> thus, missing the unique problem of impaired foot perfusion among patients with diabetes. Limb salvage in patients with diabetes and ischaemic foot ulcers requires more than revascularization. Aggressive, multi-disciplinary care should always be provided as explained earlier, including aggressive treatment of infection, local ulcer treatment, and debridement, together with invasive revascularization when possible, to improve outcomes.<sup>1, 87</sup>

### *Endovascular treatment vs. open reconstructive surgery*

Open reconstructive surgery has been the gold standard in lower extremity revascularizations in patients with diabetes and CLI. Endovascular techniques have significantly evolved and gained increasing acceptance during the past decades. Together with a broad spread of the requisite skills among vascular specialists and improved balloon catheters, subintimal angioplasty and stent techniques, they have made very distal interventions on the foot possible, thereby improving outcomes and preventing restenosis.<sup>83, 176</sup> Endovascular treatment of PAD has been widely accepted as a first approach strategy due to its low mortality and morbidity, as well as its lower cost compared with bypass surgery. However, there is a risk for late failure of percutaneous transluminal angioplasty (PTA), mainly due to elastic recoil, dissection or disease progression, whereas fracture and re-stenosis of stents may occur due to deformation and mechanical compression.<sup>177</sup> Most studies on revascularization in patients with ischaemic DFUs

focus on outcomes, usually limb salvage, after a specific invasive vascular intervention.<sup>101, 175, 178</sup>

In a systematic review of the effectiveness of revascularization in patients with diabetes, PAD, and foot ulcers, which included 49 studies, the median limb salvage at 1 year after open reconstruction was 85% compared with 78% after endovascular treatment.<sup>37</sup> The overall ulcer healing at 1-year follow-ups reported in seven studies with endovascular treatment and 2 studies with open surgery was 60%. The median incidence of 30-day, or in-hospital, mortality was 1.4% following open surgery compared with 0.5% after endovascular treatment. The median overall mortality incidence at 1 year and 5 years were 13.5% and 46.5%, respectively.

*The Basil study (Bypass versus Angioplasty in Severe Ischemia of the Leg)* is the only RCT to date that compared open reconstructive surgery with endovascular treatment as a first strategy in patients with severe limb ischaemia.<sup>174, 179, 180</sup> In this study, 452 patients (42% of whom had diabetes) were included and assigned either to open surgery (n=228) or endovascular treatment (n=224) groups. Overall, there were no significant differences in the amputation-free survival or overall survival rate between the two treatment arms. However, for those patients who survived for at least two years after randomization, open surgery as a first revascularization strategy, was associated with a significant increase in subsequent overall survival and a trend towards improved amputation-free survival.<sup>180</sup> Furthermore, open surgery with vein grafts was superior to open surgery with prosthetic grafts, in term of long-term survival.<sup>179</sup> Thus, patients with severe limb ischaemia who are likely to live longer than two years are better served by vein bypass surgery as a first revascularization strategy.

The choice of the vascular intervention in patients with diabetes and CLI is usually based on patient risk, arterial anatomy, vein graft availability and the extent of tissue destruction. However, the decision is always at the discretion of the vascular surgeon.

# Aims

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The overall aims of this thesis were to study the outcome of foot ulcers and to identify factors related to outcomes in patients with diabetes and PAD that were presented and treated at a multidisciplinary foot centre.

## **Specific aims**

- I. To identify factors related to the healing of foot ulcers in patients with diabetes and severe PAD, irrespective of revascularization.
- II. To examine the outcomes and factors related to the healing of foot ulcers in patients with diabetes and severe PAD who did not undergo revascularization.
- III. To examine the relationship between the time to revascularization and the probability of healing without major amputation in patients with diabetes and ischaemic foot ulcers.
- IV. To study new ulcerations and amputations in the same foot, as well as the survival rate, in patients with diabetes and severe PAD after the healing of a foot ulcer without major amputation, irrespective of revascularization.

# Subjects and methods

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## Subjects

Patients presenting consecutively with diabetes and foot ulcers at or below the ankle that were admitted to a multidisciplinary foot centre between 1984 and 2006 were prospectively included, treated, and followed up according to a standardized protocol until healing or death. The study was designed to follow every patient for five years after intervention regarding the recurrence of ulcerations, new ulcers, amputations, and death. The study was approved by the local ethics committee.

In **Paper I**, 1,151 patients were included, irrespective of revascularization. In **Paper II**, 602 patients who did not undergo revascularization (angioplasty or open reconstructive vascular surgery) were included. All patients continued with conservative treatment at the diabetic foot clinic according to the local programme. The number of patients studied in **paper II** is smaller than the number mentioned in **paper I** because data was acquired retrospectively through patients' files. In **Papers III and IV**, out of the 1,151 patients in **paper I**, patients who were included more than once due to new ulcerations, only the first presentation at baseline, named the previous ulcer, was considered (n=1,072). In **Paper III**, 478 patients out of the 1,072 patients who had had revascularization (angioplasty or open reconstructive vascular surgery) were included. In **Paper IV**, among those 1,072 patients, patients who healed primarily or after minor amputation (n= 602) from the previous ischaemic foot ulcer were included prospectively and had an additional follow-up regarding new ulcerations on the same foot, new amputations, healing from new ulcer/ulcers, as well as survival. The follow-up in **paper IV** continued until the end of December 2012 for patients who were still alive. Medical records were used to collect data retrospectively on patients who had no further contact with the foot centre after healing of their primary foot ulcer (Figure 3).



## **Inclusion criteria**

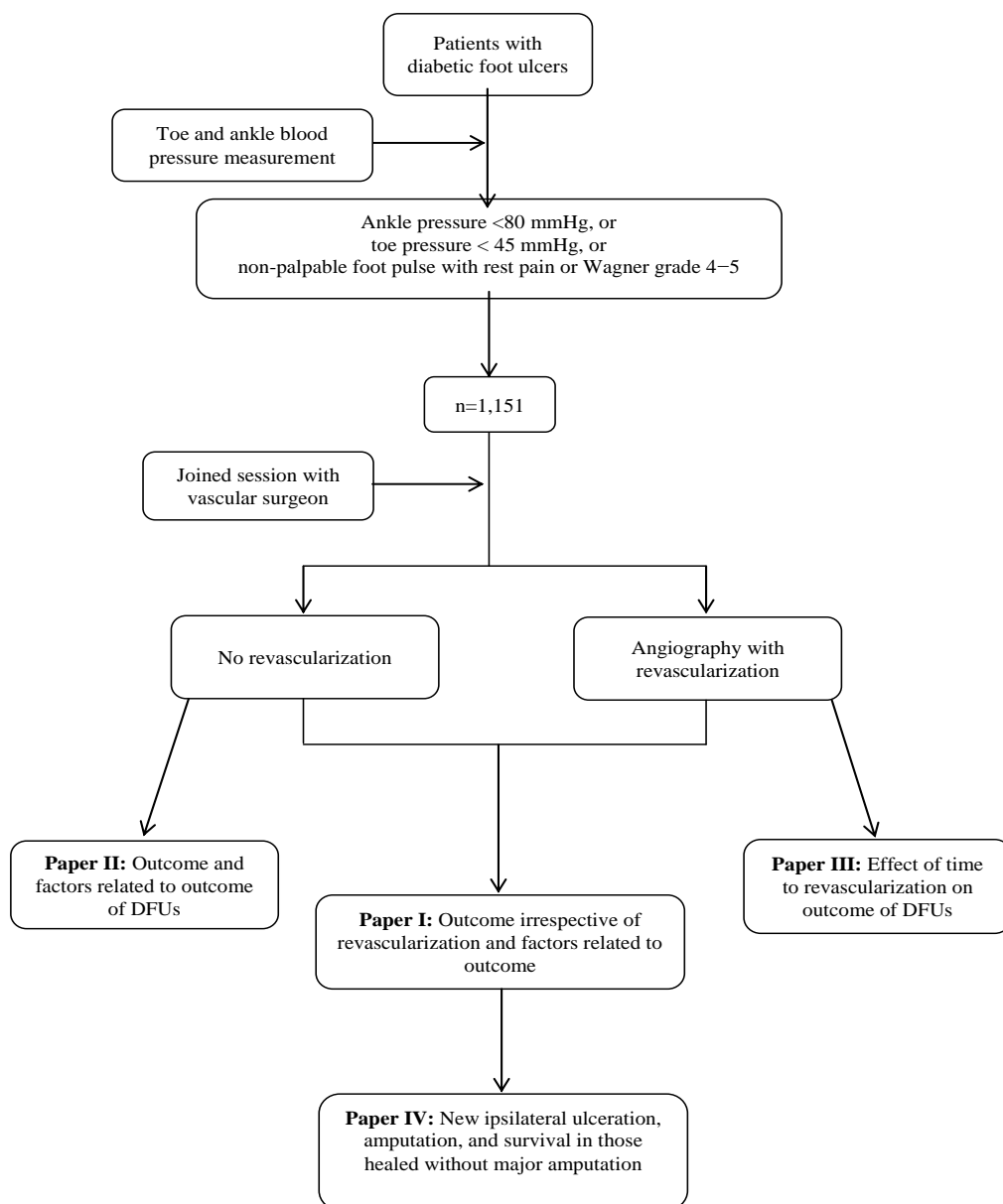
In **Papers I–III**, patients with diabetes mellitus, foot ulcers (Wagner grade 1–5, at or below the ankle) and systolic toe pressures <45 mmHg and/or systolic ankle pressures <80 mmHg were included. In case of non-measurable pressure levels, patients with non-palpable foot pulses with an ulcer of Wagner grade 4–5 or pain at rest were included. Rest pain was defined as severe persistent pain localized to the foot and relieved by lowering of the foot. All patients fulfilled Fontaine grade 4.<sup>181</sup> In **Paper IV**, inclusion criteria were patients who healed from the primary ulcer without major amputations regardless of revascularization.

## **Study design**

Patients were followed and treated according to a pre-set protocol by a multidisciplinary team, both in and out of the hospital, until healing with, or without, amputation was achieved, or until the patient died with an unhealed ulcer. All lesions were assessed and documented by the same team. Outpatient treatment was conducted in collaboration with the primary health care and home nursing services. Physical examination of the foot was performed at inclusion, and regularly during the study, by the multidisciplinary team. The core team consisted of a diabetologist, an orthopaedic surgeon, an orthotist, a podiatrist and a registered nurse educated in diabetes. Vascular investigation was conducted according to a prescheduled program by a vascular surgeon integrated in the team on a regular basis. Specially trained casting technicians provided continuous service for total contact casting. A specialist in infectious disease was available for consultations when required. All data were recorded on standardized case record forms; these forms were both computerized and transformed into files. At study entry, data were collected on previous management, referral, patient characteristics, comorbidities, ulcer characteristics and laboratory investigations.

Each patient was represented by one lesion below the ankle. Patients with several concurrent lesions were represented by the one with the worst outcome. Patients with three or more ulcers on the same foot were classified as having multiple ulcers. The most superficial ulcer included was a lesion penetrating the full thickness of the dermis (Wagner 1). The Wagner grade at inclusion and the maximal Wagner grade reached during the study period were recorded. Minor gangrene was categorized as Wagner grade 4; major gangrene was categorized as Wagner grade 5.

In **Paper IV**, the Wagner grade of the primary foot ulcer and the maximal Wagner grade reached during follow-up for the primary foot ulcer were recorded. All participants, during and after healing of the primary foot ulcer were provided with



**Figure 3.** The flow chart of the study.

adjusted shoes and individually fitted insoles for outdoor and indoor use, and were recommended for regular chiropody.

### *Definitions*

An ulcer was defined as a skin lesion, with or without necrosis, penetrating the full thickness of the dermis. Gangrene was defined as a continuous necrosis of the skin and underlying structures (muscle or bone), indicating irreversible damage that would be unlikely to heal without the loss of some part of the extremity (Wagner grades 4–5).<sup>4</sup> Major gangrene (Wagner grade 5) was defined as gangrene involving most of the foot.

### *Cardiovascular diseases*

Hypertension, angina pectoris, myocardial infarction, congestive heart failure, non-ischaemic heart disease, and cerebrovascular disease were defined as previously described.<sup>88</sup> Diabetic retinopathy was recorded after retinal photography by an ophthalmologist. Diabetic nephropathy was considered to be present at persistent urine albumin levels >300 mg/L.<sup>88</sup>

Outcomes were classified as (1) primary healing, defined as healing without any amputation with intact skin for six months or intact skin at the time of death; (2) minor amputation, defined as amputation of one or more toes or some part of the foot at or below the ankle; (3) major amputation, defined as amputation above the ankle;<sup>182</sup> and (4) death unhealed, defined as death without healing with or without any amputation.

Peripheral oedema was considered present when swelling of the foot was so pronounced as to leave an imprint after pressure by a finger. Deep foot infections (Wagner grade 3) included osteomyelitis/osteitis, deep foot abscesses and purulent soft tissue infections. All patients considered to have osteomyelitis had an open lesion fulfilling at least three of the following criterion: cellulitis, positive bacterial culture, radiological and/or scintigraphic evidence, and pathologic anatomic diagnosis.<sup>183</sup>

Rest pain was defined as severe persistent pain localized to the foot and relieved by lowering of the foot. Claudication was defined as recurrent cramping pain or tightness in the calf that was induced by exercise and relieved by rest.<sup>184</sup> Ischaemic/neuroischaemic ulcers were considered present at ankle pressures <80 mm Hg or toe pressures <45 mm Hg or at Wagner grades 4 to 5 if distal pressure was not obtained.<sup>185</sup>

### *Management/Treatment*

The patients were treated as outpatients, although in cases of deep infection associated with septic conditions, foot surgeries, amputations, vascular surgeries, or exacerbations of intercurrent disease, they were treated as inpatients under the

supervision of the foot team. Patients were offered medical treatment to improve metabolic control and optimize treatment of comorbidity.<sup>1</sup> When needed, patients were also given supplementary nutrition and rehydration treatment.<sup>186</sup> When clinical signs of infection were present, oral treatment with antibiotics was provided, often according to ulcer microbiological cultures, by combining cephalosporin, quinolone or metronidazole with dicloxacillin or clindamycin. Patients with deep abscesses or acute osteomyelitis were hospitalized and intravenous antibiotics were administered.<sup>187</sup> The use of a differentiated program for analgesia was related to the cause and intensity of pain.

### *Surgical treatment*

Surgery was performed when deemed necessary by an orthopaedic surgeon. Local surgical debridement of the lesions was performed when required. Whenever an absence of infection and pain so allowed, dry necroses were left to mummify. Incision and drainage were mandatory in case of a deep plantar abscess, and resection was performed in cases of osteitis/osteomyelitis not responding to antibiotic treatment.

Amputation was performed at the discretion of the orthopaedic surgeon, according to a pre-set protocol in which the indications were progressive gangrene, a septic condition and rest pain not responding to conservative treatment. A non-healing ulcer was not considered to be an indication for amputation. The level of amputation was chosen on clinical grounds to be the most distal level possible in which healing could be anticipated, the minimal requirement being intact skin with no signs of local infection or severe ischaemia. The lowest level used for amputation was at the metatarsophalangeal level. All indications for amputation were recorded according to protocol. Resection of less than the distal phalanx was not considered an amputation.

### *Off-loading*

All patients were offered off-loading equipment adjusted to their individual needs. Protective or therapeutic shoes for indoor and outdoor use and individually fitted insoles were used in the majority of patients. In cases of plantar or heel ulcers, total contact casting was used when appropriate. Specially made orthotic appliances (orthoses) were used in cases of severe mid-foot or ankle deformities. Off-loading by crutches or wheel chairs was occasionally used.

### *Topical treatment*

According to the individual wound bed condition, different topical treatments were prescribed in written form by the multidisciplinary team. Dressing changes were performed under supervision of a registered nurse in the primary health care or home nursing services. The team maintained daytime telephone service for support five days per week. The most commonly used dressings were foam dressings,

hydrofibers, hydrogels, silicon nets, or hydrophobic gauzes. Silver and Cadexomere iodine were used as topical antimicrobial agents when appropriate. External compression bandages or intermittent compression therapies were used in the presence of peripheral oedema.<sup>1</sup>

## Measurements

Systolic toe and ankle blood pressure was measured using strain gauge and Doppler techniques at the vascular laboratory.<sup>185</sup> Systolic toe and ankle pressure were measured only at inclusion for the primary foot ulcer. In **Paper IV**, no measurement was performed after healing from the primary foot ulcer or at the development of new ulceration. Signs of sensory polyneuropathy were tested using a biothesiometer (BioMedical Instruments, New Burry, Ohio, USA) and defined as biothesiometer values  $\geq 25$  V.<sup>188</sup> At the time of the design of the study, vibratory pressure threshold measured by biothesiometer was the most commonly used technique to establish the presence of sensory polyneuropathy, and it was routinely used in our centre to screen for neuropathy in the foot, as it predicts subsequent ulceration, although it does not evaluate all modalities of neuropathy.<sup>1</sup>

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## Vascular intervention

Angiography was performed at the discretion of a vascular surgeon. A retrograde aorto-femoral angiography, routinely visualizing distal vessels as well as the pedal arch, was performed if the medical condition allowed and if informed consent was given by the patient. The catheter was placed as far distally as possible and delayed and magnified lateral foot views were routinely obtained. The popliteal and crural arteries were selectively catheterized if possible. Simultaneous percutaneous transluminal angioplasty (PTA) was performed when possible.

Exclusion criteria for angiography were:

- Medical condition not allowing angiography.
- Extensive gangrene (Wagner grade 5), but not ulcer location.
- Major amputation performed before angiography.
- Subjective life expectancy of the patient <6 months.
- Signs of ulcer healing before angiography.
- Lack of walking capacity before occurrence of ulcer, restitution not expected.
- Informed consent for angioplasty refused.

All reasons for not performing vascular interventions after angiography were registered. All patients undergoing angiography, with or without PTA, were treated, before and after intervention, according to a program regarding hydration and choice of pharmaceutical drugs to avoid renal failure.<sup>189</sup> Afterwards, patients with PTA were placed on a low molecular heparin regimen for a minimum of three months.<sup>190</sup> All patients were treated with acetylsalicylic acid or clopidogrel if no contraindication was present.

In patients for whom PTA was not possible or not successful, reconstructive surgery was considered and performed at the discretion of the vascular surgeon, provided their medical condition allowed surgery and informed consent could be obtained. Distal reconstructive surgery was defined as a bypass to or distal to the truncal tibiofibular artery. Postoperative care and follow-up were performed in cooperation and supervision by the team according to the program. Patients not available for angiography or revascularization after angiography were considered for treatment with low molecular heparin or ketanserin, if feasible, according to comorbidity.<sup>190, 191</sup> All patients, irrespective of intervention, were followed by the team according to protocol until a final outcome. In **Paper III**, the time to revascularization was calculated from first presentation at the diabetic foot centre, as the time from the onset of the ulcer was often unknown.

## Statistical analysis

Values are given as the median and range in **Papers I, II, and IV**. In **Paper III**, values are given as the median and interquartile range (IQR). Comparisons between groups were made using the Mann-Whitney or chi-squared ( $X^2$ ) test, as variables were not normally distributed. Statistical significance was defined as a p value < 0.05.

In **Papers I, II and IV**, simultaneous influence of possible risk factors on a binary outcome (primary healing and amputation or unhealed in paper I, primary healing or minor amputation vs. major amputation or unhealed in paper II, development of new ulcers or not in paper IV) was investigated by means of backward logistic regression analysis. In **papers II and IV**, all variables in the Mann-Whitney or chi-squared tests with a p-value < 0.15 were included as covariates in the regression analysis.

In **Paper III**, the Cox proportional hazard regression (method backward stepwise, lr) was used to estimate the independent effect of the waiting time to invasive vascular intervention on the ulcer healing. The time to revascularization from arrival to the clinic was entered as a categorical variable (1 ≤ 8 weeks, 2 > 8 weeks). All variables in Mann-Whitney or chi-squared tests with a p-values < 0.15

were included as covariates in the analysis. The analysis was adjusted for the type of invasive vascular intervention. Patients in the reconstruction surgery group who had only exploration (n=15) were excluded from this analysis.

In **Papers II–IV**, univariate survival analysis of the statistically significant variables in the regression models was performed using Kaplan-Meier analysis, in which statistical significance was determined by a log-rank test.

Statistical analysis was performed using SPSS version 14.0 (SPSS, Chicago, Illinois, USA) in paper I. In Paper II, SPSS statistics 20 was used, and in papers III and IV, SPSS version 21.0 (IBM Corporation, Armonk, New York, USA) was used.

# Results

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## Paper I

One thousand one hundred fifty-one patients were included in the study. After five dropped out, 1,146 continued to follow-up in the study (2 years, 0.5–5). Out of these (median age 75 years, 40–92), 61% were males, 69% were treated with insulin and 18% were smokers. IC was present in 26% of patients and pain at rest in 52%. Systolic toe pressure <45 mm Hg and an ankle pressure <80 mmHg were seen in 82% and 49% of the patients respectively (Table 5).

In 345 patients (30%), no angiography was performed (Figure 4), while 801 patients had an angiography. Among those who did not have angiography, 14 patients were excluded (dropped out). Patients who did not have an angiography continued with conservative treatment at the diabetic foot clinic according to the program.

### *Vascular interventions and outcomes*

To evaluate outcomes, patients were divided into four groups: those who did not undergo angiography (n=345), those treated with PTA (n=314), those treated with reconstructive vascular surgery (n=190), and those who received medical treatment only after angiography (n=297). Forty-six patients were lost to follow-up after angiography and 34 had not reached the end point (healing with or without amputation or death).

In total, 36% of patients healed primarily, 16% healed after minor amputation, 13% healed after a major amputation, and 27% died unhealed. The median time to healing was

27 weeks (1–292 weeks). Among patients with non-measurable peripheral ankle pressure (n=110), primary healing was seen in 36 patients (32.7%), minor amputation in 15 patients (13.6%), major amputation in 13 patients (11.8%), 44 patients (40%) died unhealed and two patients dropped out (1.8%). At the end of the study, there was a dropout rate of 5%, and 3% of patients were still in treatment (unhealed). Out of the surviving patients, 72% healed without a major

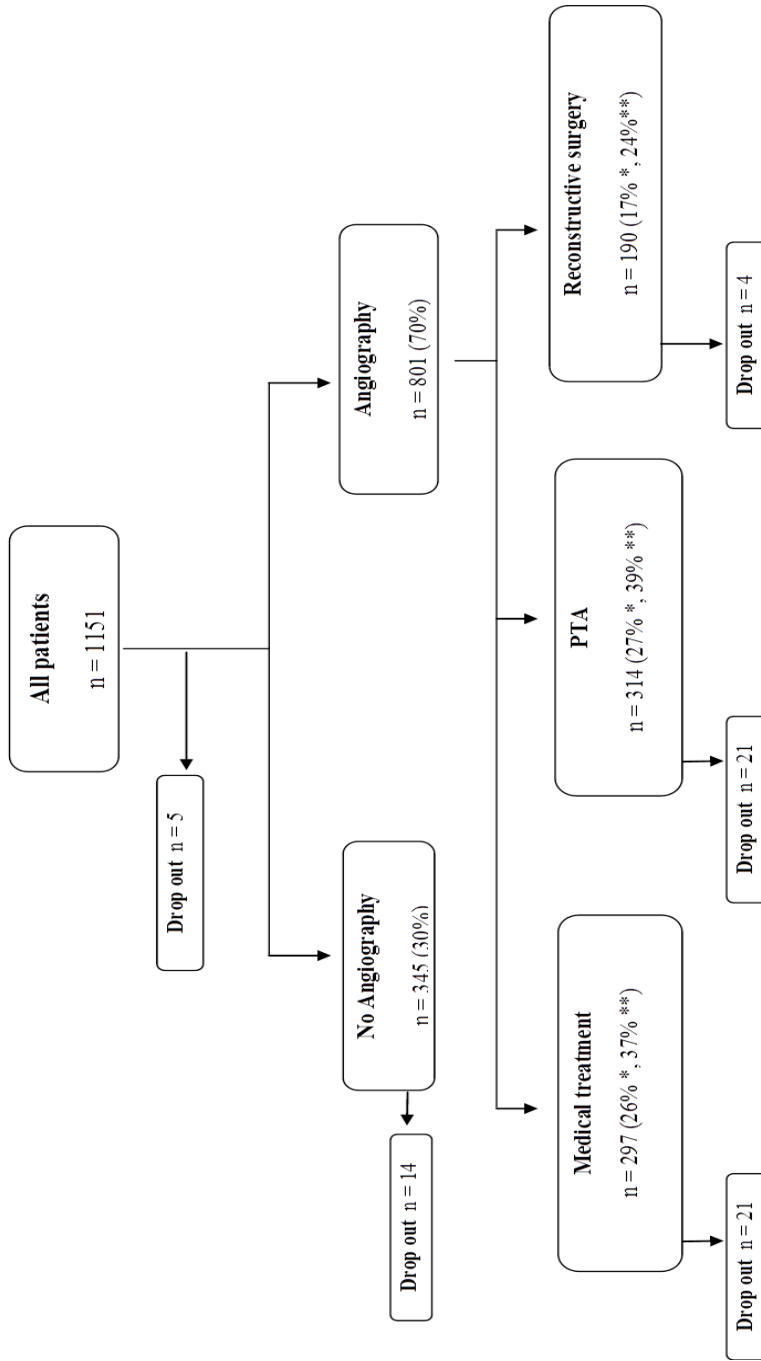


amputation (Table 6). The indications for major amputations in this study were; progressive gangrene in 68% of patients, pain in 64%, infection in 26%, acute occlusion in 4% and other reasons in 32% (unpublished data).

#### *Factors related to outcomes*

A multiple regression analysis was performed, to identify factors, including factors of demographic data, clinical characteristics, comorbidities and local characteristics, related to primary healing (Table 7). PTA and vascular surgery increased the probability of primary healing, with odds ratios (OR) of 1.77 and 2.05, respectively. The severity of PAD, age, comorbidities (congestive heart disease and/or renal impairment) and the extent of tissue destruction at inclusion were also related to the probability of healing.

In summary, in this large prospective study of individuals with diabetes, foot ulcers, and severe PAD treated at a multidisciplinary foot centre, the healing rate without major amputation in surviving patients was 72%. The probability of healing without amputation was strongly related to the severity of PAD, comorbidities, and extent of tissue destruction. Angioplasty or reconstructive vascular surgery seemed to increase the probability of healing.



**Figure 4.** Flow chart of paper I population with regard to angiography, percutaneous transluminal angioplasty (PTA), and vascular reconstructive surgery performance. \*Of all cases; \*\*after angiography.

**Table 5.** Clinical characteristics of the subjects.

	All patients (n=1,146)	No angiography (n=345)	Angiography (n=801)	p <sup>1</sup>	Medical treatment (n=297)	PTA (n=314)	Reconstructive surgery (n=190)	p <sup>2</sup> /p <sup>3</sup>
Age (yrs)	75 (40-92)	77 (46-87)	74 (40-92)		75 (44-90)	74 (44-90)	72 (46-92)	
Male sex	61% (700)	59% (203)	62% (495)		63% (186)	63% (117)	58% (111)	
Duration of diabetes (yrs)	15 (0-58)	15(1-58)	15 (0-56)		15(0-48)	16 (1-56)	15 (1-54)	
Insulin therapy	69% (786)	62% (213)	71% (569)	**	67% (200)	73% (229)	73% (138)	
HbA1c (%)	7,6 (3,6-16,0)	7,5 (4,3-14,3)	7,7 (3,6-16,0)		7,6 (3,6-15,1)	7,6 (4,3-16,0)	7,9 (4,3-12,4)	
Serum creatinine (μmol/l)	139 (41-1101)	149 (43-996)	135 (41-1101)		137 (46-755)	137 (43-883)	123 (41-1101)	
Current smokers	18% (204)	16% (53)	19% (151)		15% (45)	17% (53)	28% (52)	p <sup>2</sup> *
Peripheral oedema	57% (638)	55% (186)	57% (452)		56% (166)	58% (177)	58% (110)	
Retinopathy	49% (557)	43% (148)	51% (405)		49% (144)	53% (165)	50% (94)	
Nephropathy	37% (419)	34% (118)	38% (299)		35% (104)	41% (129)	34% (65)	
CVD	33% (337)	41% (143)	29% (234)	***	30% (89)	29% (90)	29% (54)	
CHF	28% (323)	30% (102)	28% (221)		28% (83)	28% (88)	26% (50)	
IHD	44% (501)	43% (148)	44% (351)		47% (138)	42% (131)	43% (82)	
Intermittent claudication	26% (303)	19% (64)	30% (239)	***	22% (66)	32% (101)	38% (72)	p <sup>2</sup> **
Rest Pain	52% (585)	35% (118)	59% (465)	***	49% (145)	63% (195)	67% (126)	p <sup>2</sup> ***
Toe pressure (mmHg)	32 (0-145)	33 (0-125)	31 (0-145)		32 (0-90)	32 (0-145)	29 (0-90)	
Toe pressure <30 (mmHg)	49% (557)	48% (164)	51% (411)		50% (148)	51% (159)	55% (104)	
Toe pressure <45 (mmHg)	82% (939)	82% (283)	81% (652)		81% (240)	81% (255)	82% (156)	
Ankle pressure (mmHg)	86 (0-235)	89 (0-235)	85 (0-230)		90 (20-230)	87 (10-215)	74 (0-160)	
Ankle pressue <50 (mmHg)	13% (148)	10% (33)	14% (115)		10% (31)	14% (43)	22% (41)	
Ankle pressure <80 (mmHg)	49% (558)	50% (172)	48% (386)		43% (127)	46% (145)	61% (116)	
Superficial ulcer	24% (276)	28% (96)	22% (179)		22% (66)	21% (67)	25% (47)	
Deep ulcer	21% (242)	23% (81)	20% (161)		19% (56)	21% (67)	20% (38)	
Abscess/osteitis	16% (181)	15% (52)	16% (130)		18% (52)	18% (57)	11% (20)	p <sup>3</sup> ***
Minor gangrene	33% (376)	27% (92)	35% (284)	**	33% (98)	36% (113)	38% (73)	p <sup>2</sup> ***
Major gangrene	6% (71)	7% (24)	6% (47)		8% (25)	3% (10)	6% (12)	
Ulcer of big toe	21%	23% (80)	21% (166)		21% (62)	21%	19% (37)	

	(247)					(67)		
<b>Ulcer of other toes</b>	24% (281)	23% (81)	25% (198)		28% (84)	24% (74)	21% (40)	
<b>Fore/midfoot plantar ulcer</b>	7% (82)	10% (33)	6% (49)		7% (21)	6% (20)	5% (9)	
<b>Heel ulcer</b>	14% (159)	19% (66)	12% (97)	*	11% (34)	11% (34)	15% (29)	
<b>Dorsal surface ulcer</b>	6% (70)	6% (19)	6% (47)		6% (18)	6% (18)	5% (9)	
<b>Multiple ulcers</b>	27% (312)	19% (66)	31% (245)	***	26% (78)	32% (101)	35% (66)	p <sup>2*</sup>

Data are % (n) or median (range), p1 = angiography vs. no angiography, p2 = medical treatment vs. PTA + reconstructive surgery, p3 = PTA vs. reconstructive surgery. \* <0.05, \*\* <0.01, \*\*\* <0.001. CVD=cerebrovascular disease, CHF=congestive heart failure, IHD=ischaemic heart disease.

**Table 6.** Outcome in relation to vascular intervention (n=1,146).

	No angiography (n=345)		Medical treatment (n=297)		PTA (n=314)		Vascular surgery (n=190)	
	n	%	n	%	n	%	n	%
<b>Primary healing (n=415)</b>	127	37	96	32	121	39	71	37
<b>Minor amputation (n=184)</b>	36	10	43	14	60	19	45	24
<b>Major amputation (n=143)</b>	33	10	45	15	34	11	31	16
<b>Deceased (n=310)</b>	128	37	84	28	63	20	35	18
<b>Drop outs (n=60)</b>	14	4	21	7	21	7	4	2
<b>Still under treatment (n=34)</b>	7	2	8	3	15	4	4	2

**Table 7.** Factors related to ulcer primary healing.

	OR (95%CI)	P-value
<b>Age &lt; 75 yrs</b>	1.03 (1.02-1.05)	<0.001
<b>Serum creatinine &lt;130 µmol/l</b>	1.59 (1.15-2.2)	0.005
<b>Ankle pressure &gt;50 mmHg</b>	1.62 (1.18-2.23)	0.003
<b>No congestive heart failure</b>	1.81(1.26-2.95)	0.01
<b>Single ulcer vs. multiple ulcers</b>	2.75 (1.93-3.92)	<0.001
<b>Ulcer of Wagner grade 1-2</b>	2.86 (2.06-3.94)	<0.001
<b>PTA</b>	1.77 (1.24-2.53)	0.02
<b>Reconstructive vascular surgery</b>	2.05 (1.33-3.16)	0.001

## Paper II

Six hundred and two patients were included (one dropped out prior to angiography) and continued to follow-up in the study (median 30 weeks, [1–276]). Patients were of older age (median 76 years, range 36–95 years), predominantly men (60%), with a median duration of diabetes of 15 years (range 0–61 years) and 16% were current smokers. IC was present in 19% of patients, rest pain in 39%, and peripheral oedema in 55%. A systolic toe pressure <45 mmHg and an ankle pressure <80 mmHg were seen in 79% and 54% of patients respectively. At inclusion, 26% of the patients had a deep ulcer of Wagner grade  $\geq 3$  compared with 53% during follow-up. Forty-two percent of all patients had an ulcer progress during the follow-up time.

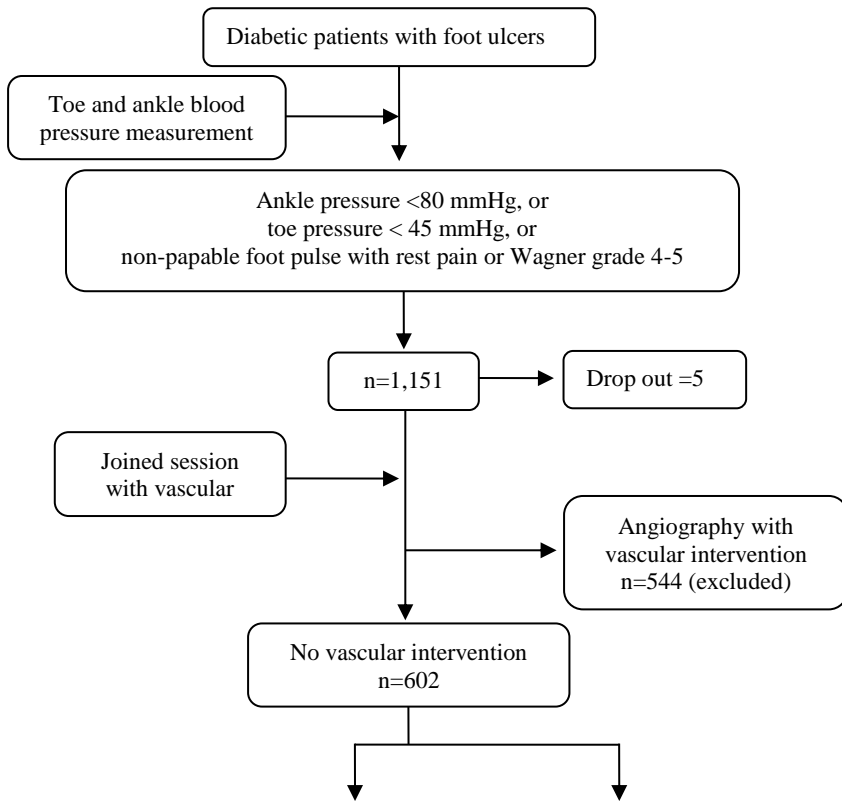
### *Angiography versus no angiography*

In 319 patients (53%), no angiography was performed according to protocol, while 283 patients had an angiography. Patients who underwent angiography were younger ( $p=0.017$ ) and had less cerebrovascular disease ( $p=0.005$ ), but had more frequent had rest pain ( $p<0.001$ ), IC ( $p=0.012$ ), maximal Wagner ulcer grade  $\geq 3$  prior to outcome ( $p=0.031$ ) and signs of ulcer progression ( $p=0.024$ ), and underwent more major amputations during follow-up ( $p=0.019$ ) (Figure 5). There was no significant statistical difference in the healing rate between the groups.

### *Outcomes*

Primary healing was seen in 38% of patients, corresponding to 56% of the surviving patients. Seventy-four percent of the surviving patients healed without major amputation. Four patients still had an on-going ulcer at the end of the study. The median time for healing without major amputation was 27 weeks (1–276 weeks). Seventeen percent of the patients required a major amputation before healing (Figure 5). This was more common following an angiography than without one ( $p=0.009$ ). Thirty-three percent of patients died unhealed. The median time until death was 29 weeks (1–256): 24 weeks (1–156) for those who did not undergo angiography and 47 weeks (1–256) for those who underwent angiography.

A multiple regression analysis of all patients was performed to identify factors, including demographic data, clinical characteristics, co-morbidities and local characteristics, related to primary healing or healing after minor amputation (Table 8). Rest pain, ankle pressure, co-morbidities (ischaemic heart disease, cerebrovascular disease, and renal function impairment) and the maximal extent of tissue destruction were related to the probability of healing.



Outcome	No angiography nr=319 (53%)	Angiography without intervention nr=283 (47%)	Total nr=602 (100%)
Ongoing ulcer	2 (-)	2 (-)	4 (-)
Primary healing	119 (37)	108 (38)	227 (38)
Healed after minor amputation	34 (11)	38 (13)	72 (12)
Healed after major amputation	40 (13)	61 (22)	101 (17)
Deceased unhealed with/without amputation	123 (38)	74 (26)	197 (33)
Drop out	1 (-)	0 (-)	1 (-)

**Figure 5.** Flow chart of the study population and outcome with regard to angiography performance.

A similar regression analysis among surviving patients showed that the same factors (rest pain, severity of peripheral arterial disease, ischaemic heart disease, cerebrovascular disease, and maximal extent of tissue destruction), with the exception of renal function impairment, were also related to the probability of healing in this group.

**Table 8.** Factors related to ulcer healing.

	All patients		Survived patients	
	OR (95% CI)	P value	OR (95% CI)	P value
<b>Pain at rest</b>	0.59 (0.38 – 0.91)	0.016	0.34 (0.14 – 0.81)	<0.0001
<b>Ankle pressure &gt;50mmHg</b>	2.44 (1.27 – 4.66)	0.007	3.73 (1.41 – 9.88)	0.008
<b>Serum creatinine &gt;130 µmol/L</b>	0.55 (0.34 – 0.88)	0.012	0.56 (0.27 – 1.17)	NS
<b>Ischaemic heart disease</b>	0.52 (0.34 – 0.81)	0.004	0.47 (0.23 – 0.94)	0.033
<b>Cerebrovascular disease</b>	0.41 (0.27 – 0.64)	<0.001	0.43 (0.21 – 0.86)	0.017
<b>Max. Wagner grades ≥3 reached</b>	0.51 (0.33 – 0.77)	0.002	0.08 (0.03 – 0.20)	<0.001

Healing=primary healing or healing after minor amputation.

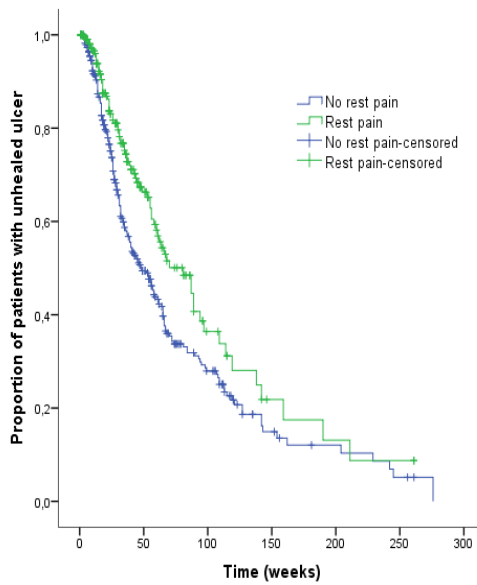
A Kaplan-Meier survival analysis was used to display survival curves for the factors that affected healing according to the regression analysis shown in Table 7. Rest pain ( $p= 0.002$ ), maximal extent of tissue destruction ( $p<0.001$ ) (Figure 6A and B), cerebrovascular disease ( $p=0.006$ ), and renal function test ( $p=0.009$ ), but not ankle pressure or ischaemic heart disease, showed significant relationships to healing over time.

#### *Outcomes in relation to the reason for not performing vascular interventions*

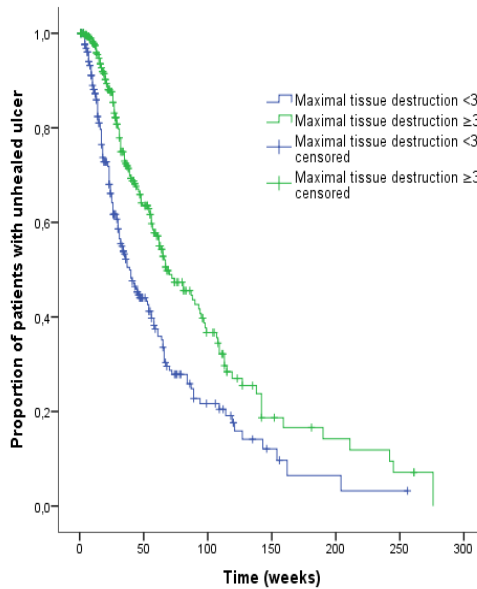
A deteriorated general condition of the patient ( $n=166$ ), lack of patient consent to angiography and further intervention ( $n=100$ ), and signs of ulcer healing ( $n= 98$ ) were the most common reasons why angiography or further vascular intervention were not performed. Fourteen patients had all arteries open in the lower leg on angiography despite the inclusion criteria. Thirteen of these fourteen patients had a toe pressure <45 mmHg; two of them had non-measurable ankle pressure.



6A



6B



**Figure 6.** Healing probability (patients' survival free from major amputation) in relation to: 6A- rest pain and 6B- maximal Wagner grade reached during study period. In tables: number of patients at risk.

Patients with signs of healing (n=98) or open arteries on angiography (n=14) all healed without major amputation, with the exception of one patient who died unhealed. Of patients with a deteriorated general condition prior to or after angiography (n=166), a lack of vein graft (n=10), or ulcer location (n=6) as reasons for not performing vascular intervention, 78% required a major amputation or died unhealed. When vascular intervention was not possible according to angiography (n=60), 43% of patients healed without major amputation. Among those who did not give consent for angiography (n=100) or those without walking capacity (n=60), healing without major amputation was seen in 59% and 55% of these patients respectively.

In summary, factors strongly related to the probability of healing without a major amputation, despite the absence of revascularization were severity of PAD, comorbidities, and the extent of tissue destruction. A primary healing rate of 38% was achieved with a corresponding primary healing rate of 56% in surviving patients. The corresponding healing rate for healing below the ankle (including minor amputations) was 50% and 74%, respectively. Seventeen percent of patients healed after major amputation and 33% of the patients died unhealed.

### **Paper III**

#### *General characteristics*

Four hundred and seventy eight patients were included. Three patients dropped out following revascularization, and 475 continued to follow-up in the study. The patients' median age was 74 years (66–80), 60% were men, with a median time of known diabetes of 15 years (10–24). IC was present in 34% of patients, rest pain in 63% and peripheral oedema in 57%. A systolic toe pressure <45 mmHg and an ankle pressure <80 mmHg were seen in 78% and 43% of patients respectively. At inclusion, 21% of patients had deep ulcers of Wagner grade  $\geq 3$ , although 50% of patients showed ulcer progression during follow-up and 55% reached a maximum Wagner grade of  $\geq 3$  at some stage during the study period. The median follow-up time until outcome was 10 months (5–16).

#### *Revascularization*

PTA was performed in 315 patients (66%). Reconstructive vascular surgery was attempted in 163 patients (34%). In 15 (9%) of these patients, a surgical exploration revealed that no further reconstruction was possible. In the remaining 148 patients, 62% (n=92) had distal procedures – tibiotruncal or below (Suppl. Table). No difference was found between patients who had PTA or reconstructive surgery regarding ulcer progression (data not shown).

### *Time to revascularization*

The median time from first presentation at the diabetic foot centre to revascularization was 8 weeks (3–18). Patients who had shorter times to revascularization ( $\leq 8$  weeks) compared with those with longer times to revascularization ( $> 8$  weeks) had more frequent peripheral oedema (62% vs. 50%, respectively,  $p = 0.025$ ) and more frequent rest pain (69% vs. 56%, respectively,  $p = 0.005$ ). The median time between diagnostic angiography and PTA was 0 week (0–0.1), while median time between diagnostic angiography and reconstructive surgery was 4 weeks (2–10).

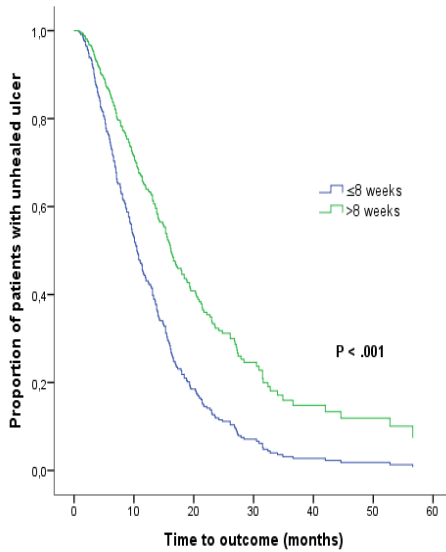
### *Outcomes*

Out of the 475 patients that continued to the follow-up, 305 (64%) healed without major amputation, 217 (45%) healed primarily and 88 (19%) healed after a minor amputation. Sixteen percent ( $n=76$ ) of the patients healed after a major amputation and 19% ( $n=92$ ) died unhealed. Two patients had an ongoing ulcer at the end of follow-up. Thus, 80% of the surviving patients healed without major amputation. The median healing time irrespective of intervention was 10 (5–16) months. The median healing time for primary healing was 8 (4–15) months, and the time for healing after minor amputation was 14 (9–20) months. Patients who healed without major amputation were younger ( $p=0.007$ ), had lower serum creatinine ( $p=0.016$ ), had less frequently congestive heart failure ( $p=0.001$ ), less frequent signs of ulcer progression ( $p<0.001$ ), and had more frequent IC ( $p=0.001$ ).

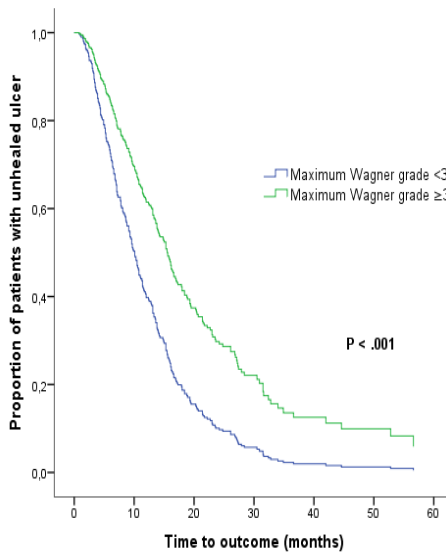
### *Factors affecting the probability of healing over time*

A shorter time to revascularization (Figure 7), a Wagner grade of  $< 3$  reached during the follow-up period (Figure 8), and the presence of IC were significantly related to a higher probability of healing without major amputation over time. The presence of peripheral oedema was significantly related to a lower probability of healing (Table 9). No statistical differences were seen between patients with and without IC regarding toe pressure or ankle pressure. However, patients with IC had less frequent peripheral oedema compared with those without IC (49% vs. 62%, respectively,  $p=0.008$ ).

Univariate survival analysis of each of these factors was performed using Kaplan-Meier analysis. Each factor; time to vascular intervention ( $p<0.001$ ), maximal Wagner grade  $< 3$  ( $p<0.001$ ), absence of peripheral oedema ( $p=0.013$ ), and IC ( $p<0.001$ ) showed a significant relationship to healing, without major amputation, over time. Kaplan-Meier analysis was performed for the time to revascularization in patients who had reconstructive vascular surgery or PTA, separately. Both groups showed a significant relationship to healing, without major amputation, over time.



**Figure 7.** Probability of ulcer healing without major amputation in relation to time to revascularization.



**Figure 8.** Probability of ulcer healing without major amputation in relation to maximal tissue destruction reached during follow up.

**Table 9.** Survival analysis for factors affecting healing probability

	<b>HR (95% CI)</b>	<b>P value</b>
<b>Intermittent claudication</b>	1.64 (1.26-2.13)	<0.001
<b>Peripheral oedema</b>	0.76 (0.58-0.98)	0.033
<b>Max. Wagner grades &lt;3 reached</b>	1.92 (1.50-2.50)	<0.001
<b>Time to intervention ≤8 weeks<sup>a</sup></b>	1.96 (1.52-2.52)	<0.001

Healing=primary healing or healing after a minor amputation. <sup>a</sup> =Time between first presentation at diabetic centre and revascularization

A similar analysis was performed for the time to revascularization for patients who healed primarily and those who healed after minor amputation. The time to revascularization showed a statistically significant relationship to both healing primarily ( $p=0.006$ ), and to healing after minor amputation ( $p<0.001$ ). Kaplan-Meier analysis was performed for the maximal Wagner grade in patients who had reconstructive vascular surgery or PTA, separately. Both groups showed significant relationship to healing, without major amputation, over time.

In summary, this study of consecutively presenting and prospectively followed patients with diabetes, foot ulcers and severe PAD, who were treated and followed by a multidisciplinary foot team, showed that the time to revascularization after admittance to the diabetic foot centre, the extent of tissue destruction, peripheral oedema, and IC were related to the probability of healing without major amputation.

## **Paper IV**

Six hundred and two patients were included and followed up after healing of primary foot ulcers either primarily ( $n=443$ , 41%) or after minor amputation ( $n=159$ , 15%). At the time of inclusion for the primary foot ulcer, the median age was 73 years (36–95) and 60% were males. Twenty nine percent of patients had IC. Out of the 602 patients, 33% ( $n=199$ ) underwent PTA, and 18% ( $n=106$ ) had open reconstructive surgery to achieve healing of the primary foot ulcer. The study time from the healing of the first primary foot ulcer among all included patients until the end of 2012 was 305 months, and the time from the healing of the last primary foot ulcer was 26 months.

### *Ipsilateral new ulcerations*

New ulcer/ulcers in the same foot, regardless of the ulcer site, developed in 34% (n=202) of patients. The median time for developing a new ulcer was 15 months (0–106). Out of the 202 patients, 150 patients (74%) developed a new ulceration only once during the observation period. In 38 patients, new ulcerations developed twice, i.e., a second new ulceration after healing of the first new ulceration. Eleven patients had a new ulceration three times, and in three patients a new ulceration occurred four times in the same foot.

No new ulcers developed in the same foot in 379 patients (63%) during the follow-up period. The follow-up time in this group was 30 months (0–110). The follow-up of these patients was frequently retrospective through patients' files. In 3% (n=21) of patients, no data regarding new ulcer development could be collected, and the patients were considered as drop outs.

### *Outcomes of new ulcers*

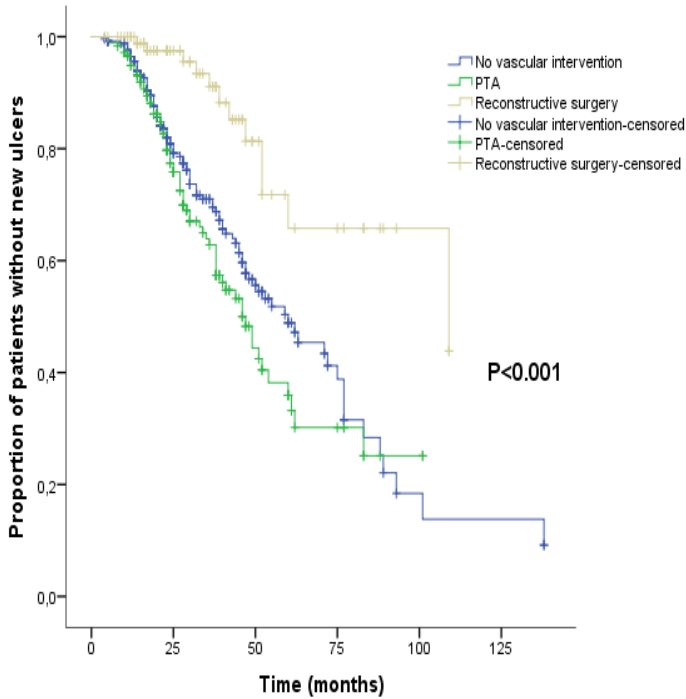
By the end of the follow-up, 52% (n=104) of patients with new ulcerations healed either primarily (72%, n=75) or after minor amputation (28%, n=29). Thirty six percent (n=73) of patients died unhealed, 8% (n=16) healed after major amputation, and 4% (n=9) were still alive with unhealed ulcers. The follow-up time in these patients since new ulcer development was 28 months (1–137).

Out of the amputations following a new ulcer development (n=45), 11 amputations (eight minor and three major amputations) were performed on patients previously healed after minor amputation.

### *Factors related to new ulcerations*

A multiple regression analysis of all patients (n=602) was performed to identify factors related to the development of new ulcers in the same foot. A maximum Wagner grade <3 of the primary foot ulcer (p=0.017, OR 0.63, 95% CI 0.43–0.92) and open reconstructive surgery (p<0.001, OR 0.26, 95% CI 0.14–0.48) were associated with lower probability for the development of new ulcers during the observation time.

A Kaplan-Meier analysis was performed to display the survival curves for maximum Wagner grade and invasive vascular intervention in relation to the probability of developing of new ulcers in the same foot. Both factors, maximum Wagner grade reached during follow-up of the primary foot ulcer (p=0.038) and reconstructive surgery (p<0.001), showed significant relationship to new ulcer development over time (Figure 9).

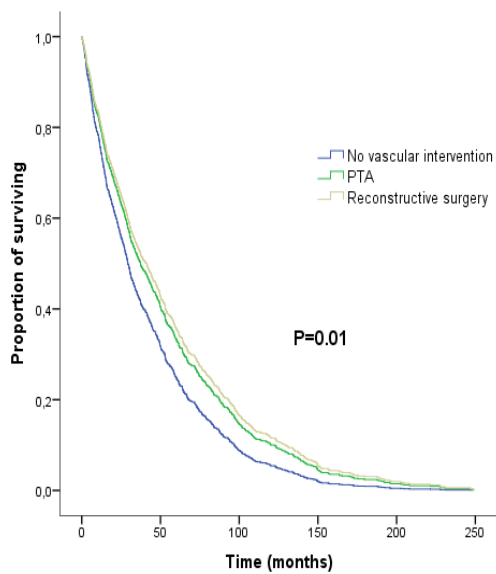


**Figure 9.** Probability of new ulceration in relation to revascularization.

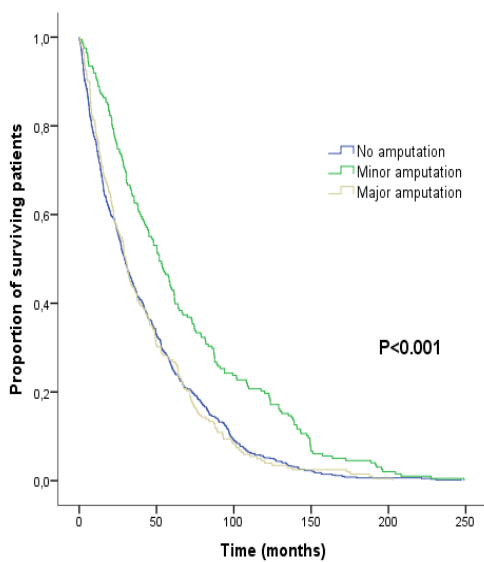
### *Survival rate*

Since healing from a primary ulcer (n=602) until 2012-12-31, the median survival of patients was 54 months, while 10% died at 17 months and 90% died at 133 months. These patients (n=602) were included from a cohort of 1,072 with a primary ischaemic foot ulcer. Out of these patients (n=1,072), 1,021 patients were deceased by the end of 2012. Their median survival (50<sup>th</sup> percentile) was 33 months, with 10% dying at five months and 90% at 107 months. A Kaplan-Meier analysis showed that invasive revascularization, including, both PTA and reconstructive surgery, was significantly associated with better survival probability (Figure 10A). A similar analysis was performed regarding amputation and mortality. Patients who had minor amputations had better survival probabilities compared with those who had major amputations or no amputation (Figure 10B).

10A



10B



**Figure 10.** Probability of surviving in relation to A: revascularization and B: amputation.



When we compared survival among patients with or without new ulcerations using Kaplan-Meier analysis, patients who had new ulcerations had better survival ( $p < 0.001$ ) compared with those who had no new ulceration.

In summary, in patients with diabetes, PAD, and healed without major amputation from previous ischaemic foot ulcers, 34% developed new ulcerations in the same foot within the observation time. Twenty two percent of patients who developed new ulcers had an amputation before healing from the new ulcers. Lower maximal tissue destruction and open reconstructive vascular surgery were related to a lower risk of new ulcerations. Patients with diabetes and ischemic foot ulcers had a median survival time of 33 months

# Discussion

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## Outcome

In paper I, we have shown that in patients with diabetes, foot ulcers, and severe PAD treated at a multidisciplinary foot centre, the healing rate without major amputation in surviving patients was 72%, irrespective of revascularization. In 13% of patients, a major amputation could not be avoided. In patients with diabetes, foot ulcers, and severe PAD not feasible for revascularization (paper II), a primary healing rate of 38% was achieved with a corresponding primary healing rate of 56% in surviving patients. The corresponding healing rate for healing below the ankle (including minor amputations) was 50% and 74% respectively. Seventeen percent of patients healed after major amputation and 33% of patients died unhealed.

Comparisons between studies are difficult due to differences in design, settings, patient selection, definitions, follow-up times, and other confounding factors. In the limited number of studies, including diabetic patients with ischaemic or neuroischaemic ulcers, the focus was on limb salvage after a specific intervention and they often included patients with and without diabetes, and with and without ulcers.<sup>101, 170, 172</sup> However, our results in regard to healing are similar to those of other studies<sup>171, 178</sup> in which healing rates ranged from 70% to 73%.

The present study was not designed to assess limb salvage, but the rate of ulcer healing in all consecutively presenting patients with diabetes and an ischaemic or neuro-ischaemic ulcer. Higher healing rates have been reported in other studies in diabetic populations with both neuropathic and neuroischaemic ulcers.<sup>34, 110, 192</sup>

There are a limited numbers of studies that have examined diabetic patients with ischaemic foot ulcers without vascular intervention. Lepäntalo et al. have previously shown, in patients with critical limb ischaemia without vascular reconstruction, that mortality at 1 year in these patients was 46% and limb survival at 1 year was 54%.<sup>95</sup> In another study, in which patients with PAD and foot ulcers were treated conservatively, major amputation at 1 year was performed in 23% of patients.<sup>96</sup> However, both studies included non-diabetic patients.

In a systematic review of the effect of revascularization in diabetic patients with ischaemic foot ulcers, median mortality after reconstructive surgery was 13.5% at 1 year and 46.5% at 5 years. However, in some of the studies included in this review, up to 20% of patients may not have had a foot ulcer, and the results did not exclude these patients.<sup>37</sup>

## Factors related to outcomes

Comorbidities (congestive heart failure and/or renal impairment), the severity of PAD (ankle pressure  $\leq 50$  mm Hg), and the extent of tissue involvement (Wagner grades 3–5 and multiple ulcers) were strongly related to a low probability for ulcer healing irrespective of revascularization. Angioplasty or reconstructive vascular surgery seemed to increase the probability of healing.

The presence of foot ulcers in individuals with diabetes has to be recognized as a sign of a multi-organ disease. This was confirmed by a substantial number of studies and is further emphasized by the present findings.<sup>88, 89, 114, 178</sup> Diabetic patients with lower limb ischaemia have been shown to have more chronic renal disease and a history of myocardial infarction compared with non-diabetic patients.<sup>193</sup> One study, in which 76% of patients without a previous history of heart disease had signs of cardiac muscle dysfunction, has shown that cardiac disease is common in patients with diabetes and chronic foot ulcers.<sup>194</sup> Patients with diabetic foot problems have been shown to have a higher prevalence of cerebrovascular accidents and a higher incidence of new cerebrovascular accidents compared with diabetic patients without foot ulcers.<sup>58</sup> Furthermore, kidney disease is also associated with worse outcomes in diabetic foot problems.<sup>28, 36, 195</sup>

We have shown in papers I–III that the extent of tissue destruction negatively affects the probability of healing. This is in agreement with previous studies.<sup>34, 35, 84</sup> Irrespective of non-invasive vascular examination results, it has been recommended to consider vascular imaging and subsequent vascular intervention in diabetic patients based on ischaemic tissue destruction if no signs of healing are noticed within six weeks of conservative treatment.<sup>83</sup> The Wagner classification system, which was used in our study, has been previously shown to be associated with healing.<sup>196</sup> Furthermore, increased Wagner staging was associated with increased healing time and amputation.<sup>197</sup> There are a number of suggested classification systems of foot ulcers.<sup>198, 199</sup> However, these systems were not available when the present study was initiated.

In paper I, PTA, frequently multi-segmental (46%) and to the crural arteries (46%), was performed in 27% of patients and reconstructive vascular surgery in 17%. In most cases, complications were related to comorbidity rather than the vascular intervention *per se*. This is in agreement with other studies.<sup>200</sup> However, we cannot compare the outcome of PTA vs. vascular surgery in the present study,

because, according to the design of the study, vascular surgery was performed in patients not suitable for PTA. In the extended follow-up of the BASIL trial, 452 patients with severe PAD were followed up for up to five years, 42% of the patients were diabetic.<sup>180</sup> In patients who survived for at least two years, vascular surgery was associated with significant increase in subsequent overall survival. Furthermore, PTA had a higher early failure rate.<sup>179</sup>

## **Outcomes in relation to why no intervention was performed**

There are commonly accepted exceptions for considering angiography or revascularization in patients with PAD and impaired foot ulcer healing, including severely ill patients, short life expectancy, pre-existing severe functional impairment, and extensive tissue destruction.<sup>59</sup> Similarly, there were different reasons why angiography or further revascularization were not performed in paper II. Signs of healing and open arteries on angiography were factors for good outcomes in which all patients healed without major amputation, with the exception of one patient who died before healing. Fourteen patients had all arteries open in the lower leg upon angiography, and thirteen of them had a favourable outcome. However, the number is too small to warrant reconsideration of the blood pressure criteria used for screening.

Moreover, a deteriorated general condition prior to angiography or vascular intervention, lack of vein graft, and ulcer location as reasons for not performing vascular intervention could be considered to be factors predictive of poor outcomes, as only 22% of such patients healed without major amputation. It has been reported that up to 40% of patients requiring a below-knee bypass will have an unusable or absent vein graft in either extremity owing mainly to prior coronary bypass or venous insufficiency.<sup>201</sup> However, it remains uncertain whether this unfavourable outcome in our study is due to the inability to improve arterial flow to the foot or to the existence of co-morbidities.

## **Effect of time to revascularization**

In paper III, we have shown that a shorter time from the first presentation to the foot team to revascularization predicts a better healing probability over time without major amputation. This is, to our knowledge, the first study that examined the influence of time to revascularization on the outcomes of ischaemic foot ulcers in patients with diabetes.

The finding was the same for PTA and for reconstructive surgery. Currently, an observation time of 4–6 weeks is recommended by the IWGDF before revascularization is considered in patients with diabetes and ischaemic foot ulcers,

irrespective of the results of the non-invasive vascular tests.<sup>83</sup> The European Society for Vascular Surgery recommends local debridement in cases of deep foot infections before considering revascularization in the same patient group.<sup>202</sup> Similarly, in the Trans-Atlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II), revascularization should be considered if clear signs of critical limb ischaemia are present or if healing does not occur despite optimal non-invasive treatment.<sup>120</sup>

In one study by Faglia E et al., regarding early debridement and revascularization in patients with diabetes and an acute deep foot infection, the authors concluded that immediate revascularization allows for an outcome similar to patients without PAD. All patients in that study had a deep foot infection, which was the primary reason for the admission. It was concluded that early surgery in regard to foot infections had a better outcomes compared with clinical observations using systemic antibiotics. The average time difference until revascularization between the two groups, immediate vs. later revascularization groups, was only six days.<sup>203</sup>

This finding regarding the time to revascularization may reflect the need to consider invasive revascularization as early as possible in patients with diabetes and ischaemic foot ulcers irrespective of the presence of pain and the extent of wound and tissue destruction at presentation

The time to revascularization in our study time was calculated from the first visit to our foot team, as the time from foot ulcer onset is usually unknown or not confirmed. A delay between the onset of a foot lesion and first treatment is common. Almost 40% of foot lesions are not detected by the patient her/himself, but by relatives or health care staff.<sup>204</sup> Furthermore, patients with diabetes who believe that pain is a reliable symptom of foot ulceration are less likely to seek early medical advice for foot care.<sup>205</sup> A delay between the initial treatment of foot ulcers and referrals to a foot clinic is also common, in which the main reasons are an underestimation of the severity of the foot lesions or a lack of recognition of ischaemia.<sup>206</sup> There is still limited information regarding factors that influence the patient's willingness to seek medical care and regarding the time delay in referral patterns and pathways to interventions, particularly in patients with diabetes and ischaemic foot ulcers.<sup>207</sup> In the Eurodial study, ulcer duration was reported at study entry.<sup>192</sup> Fifty seven percent of patients had ulcer durations of 1 week to 3 months, and in 27% of patients, ulcer duration was >3 months. Ulcer duration was associated with a risk of non-healing. However, the study did not mention whether the ulcer duration was since ulcer development or presentation to a health care provider. In a large Swedish study, Gershater M et al. reported an estimated ulcer duration of 11 weeks (range 0–350), which had no significant effect on ulcer outcomes.<sup>34</sup>

## New ulcerations and amputations

In paper IV, we have shown that in patients with diabetes and PAD, and who healed without major amputation from a previous ischaemic foot ulcer, 34% developed a new ulceration in the same foot within the observation time. Twenty two percent of patients who developed new ulcers had an amputation before healing from the new ulcers. Maximal tissue destruction and open reconstructive vascular surgery were related to a lower risk of new ulcerations.

Several studies have examined foot ulcer recurrence in patients with diabetes.<sup>97, 100, 208, 209</sup> Apelqvist J et al. showed that 50% of patients had new ulcers within two years.<sup>97</sup> Pound N et al. showed that 40% of patients had new ulcerations after a 31-month follow-up.<sup>100</sup> However, these studies included both neuropathic and neuroischaemic foot ulcers. Furthermore, they included ulcers from the contralateral foot or ulcers that developed after healing from major amputations.<sup>97</sup> Thus, the results of these studies cannot be compared to the present study. In a systematic review of the effectiveness of revascularization, usually limb salvage is reported, rather than ulcer healing, as outcome, and there were no reports on new ulcerations in relation to revascularization.<sup>37</sup> The published data on ipsilateral new ulcerations are very limited. In one study by Faglia E et al, only 13% of 115 patients with diabetes developed new ulcerations; 50% of them were ipsilateral.<sup>98</sup> It is also worth mentioning that 16% of patients had no PAD. New ulcerations in this study were not associated with any of the clinical variables investigated. However, the extent of tissue destruction and revascularization were not included. In a recent study showed that, similar to our results, 33.5% of patients with type 2 diabetes that healed from previous foot ulcers after minor amputations (n=185) developed a new ulcer in the same foot within five years of follow-up. However, 15% of patients did not have PAD and an absence of foot pulses was a criterion for diagnosing PAD.<sup>210</sup>

In the present study, reconstructive surgery, irrespective of primary healing or healing after minor amputation, predicted fewer new ulcerations in the same foot. No similar prediction was found for PTA. In a study by Scatena A et al., revascularization in patients with DFUs and critical limb ischaemia were significantly associated with fewer ulcer recurrences.<sup>211</sup> Ulcer recurrence was seen in 11.8% (n=29) of included patients, 4 (1.6%) in PTA patients, 2 (0.8%) in patients who had undergone open reconstructive surgery, and 23 (9.4%) in patients who had medical therapy only.

In the present study, we did not find a significant difference between reconstructive surgery and PTA regarding baseline clinical characters, which may explain why only reconstructive surgery was related to a lower rate of new ulcerations. However, new ulcerations in our study were not ulcer recurrences, as they included new ulcerations in other sites of the ipsilateral foot. Furthermore, in the present study, data regarding patency after revascularization were not

evaluated. Thus, the failure rate cannot be estimated and the healing of ulcers among these patients is not necessarily a result of revascularization. Endovascular revascularization in our study did not necessarily directly target artery/arteries supplying the ulcer area, which has been shown to be associated with improved healing and limb salvage.<sup>212-214</sup>

Reconstructive surgery has been shown previously to result in faster and better healing for foot ulcers larger than 2 cm in size compared with endovascular revascularization.<sup>215</sup> In the BASIL study, the only RCT that compared reconstructive surgery and PTA in patients with severe limb ischaemia, patients who survived >2 years after reconstructive surgery had better overall survival and showed a trend to better amputation-free survival compared with PTA.<sup>216</sup> In the present study, we cannot compare reconstructive surgery and PTA regarding outcomes or new ulcerations as the study was designed to perform PTA initially, and reconstructive surgery was considered if PTA was not possible.

The extent of tissue destruction in previous ulcers, using Wagner's classification system, was found in the present study to predict new ulcerations. The Wagner classification system has previously been shown to be associated with healing.<sup>196</sup> Furthermore, increased Wagner staging was associated with increased healing time and amputation.<sup>197</sup> There are a number of suggested classification systems of foot ulcers.<sup>198, 199</sup> However, these systems were not available when the present study was initiated. The development of new foot ulcers in patients who healed primarily or after minor amputation from previous extensive tissue destruction may be due to an already existing or developing deformities or functional disability in the same foot which increase the risk for new ulcerations. Amputation of the great toe has been shown recently to be an independent risk factor for new ulcerations after healing.<sup>210</sup>

In paper IV, we have shown a high risk of amputation after new ulcerations (22%). Thirty six percent of these new amputations were major amputations. Our results are higher compared with previously reported figures.<sup>98, 217</sup> However, these studies included patients with and without PAD. In the present study, we reported on new amputations after new ulcerations, thus we included even first time amputations. New amputations in our study, after previous minor amputation, were only observed in 5% of patients.

## **Survival**

Patients with diabetes and ischaemic foot ulcers had a median survival of 33 months. This is shorter than the survival rate reported previously for a similar patients group.<sup>218</sup> Moulik PK et al. reported a 55% mortality at five years in patients with diabetes and ischaemic foot ulcers.<sup>219</sup> We have also shown that healing without major amputation seemed to be associated with a better survival

rate. Almost 75% of patients who did not heal in our study died unhealed. This may explain why patients with new ulcerations had better survival in our study. It has been shown that patients with diabetes and foot ulcers have higher mortality of all-causes compared with those without foot ulcers,<sup>103, 220</sup> and coronary artery disease is probably the most common cause of death.<sup>54, 208</sup> Long-term mortality is even higher among patients with PAD and renal insufficiency.<sup>209</sup>

In the Swedish health care system, due to its geographic responsibilities and reimbursement system, it is possible to follow-up patients until a specific end point, irrespective of the care provider.<sup>221</sup> This allowed the authors to follow and obtain information on patients who dropped out.



# Conclusions

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- Comorbidities, the severity of PAD and the extent of tissue involvement were the most important factors that negatively affected the probability of healing in patients with diabetes, foot ulcers and severe PAD. A higher probability of primary healing was seen in those who had vascular intervention. This indicates the value of revascularization in patients with diabetes with ischaemic or neuroischaemic ulcers to achieve healing.
- Patients with diabetes, foot ulcer and PAD considered not feasible for revascularization are not excluded from healing without major amputation. The probability to achieve healing is strongly related to co-morbidities, the severity of PAD and the extent of tissue destruction at the time of vascular evaluation. These factors, in addition to anatomical criteria, should be considered when making decision regarding vascular intervention.
- A shorter time to revascularization and less tissue destruction positively affect the probability of healing over time of ischaemic foot ulcers in patients with diabetes. This highlights the need to prioritize investigations and revascularizations in patients with diabetes and severe peripheral ischaemia to improve the outcomes of foot ulcers.
- Patients with diabetes, severe PAD and a previous foot ulcer are at high risk of developing new ulcers and undergoing amputation on the same foot after healing, indicating that continuing follow-up is essential after the initial healing of an ulcer. The extent of tissue destruction of a previous ulcer and open reconstructive vascular surgery affected the probability of developing a new ulceration.

# Limitations of the study

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- A potential negative selection bias has to be taken into account because the patients were admitted to a university-based foot centre, whereas it cannot be excluded that a few, and possibly many, superficial ulcers were treated in primary health care centres without the knowledge of the foot team. However, no exceptions were made with regarding age, comorbidities, or expected survival.
- The clinical characteristics and variables included in the study such HbA1c and serum creatinine levels, were registered at baseline without further follow-up during the study period.
- Comparisons with other studies are difficult owing to differences in design, patient selection, outcome definitions, follow-up times, and other confounding factors. Comparison with other studies is further hampered by the fact that most studies reported outcome after a specific intervention or in a mixed population of patients with and without diabetes.
- In the present study, we did not compare the outcome after PTA with that after open reconstructive vascular surgery, as, according to the design of the study, PTA was performed as an initial choice of treatment, and open reconstructive vascular surgery was performed in patients not considered feasible for PTA.
- The study had a long inclusion time, from 1984 to 2006. During that time, new treatments in foot ulcer care were introduced, including local treatments, antibiotics, anticoagulants, radiological examinations and endovascular techniques.

# Populärvetenskaplig sammanfattning

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Syftet med de fyra delarbeten som presenteras i denna avhandling var att studera dels utfall av fotsår samt identifiera faktorer relaterade till utfall och dels risken för att utveckla nya sår efter läkning av tidigare sår hos patienter med diabetes, fotsår och uttalad perifer kärlsjukdom.

Patienter med diabetes och fotsår med ett systoliskt tåtryck <45 mmHg eller ett ankeltryck <80 mmHg som uppsökte och behandlades av ett multidisciplinär diabetes fotteam inkluderades prospektivt och behandlades enligt ett vårdprogram. Alla patienter följdes upp kontinuerligt till läkning eller död oberoende av kärlkirurgisk åtgärd (revaskularisering).

Trettiosex procent av patienterna läkte primärt, 16% efter mindre amputation (amputation genom eller nedom fotleden), 13% efter större amputation (amputation ovanför fotleden) och 27% dog oläkta. Hos patienter utan revaskularisering, läkte 38% primärt, 12% läkte efter mindre amputation, 17% läkte efter större amputation och 33% dog oläkta. Samsjuklighet, svårighetsgraden av perifer kärlsjukdom och graden av sårskada var starkt relaterade till sämre sårhäkning oavsett revaskularisering. Tiden från ankomsten till diabetes fotteamet till revaskularisering var också relaterad till sannolikheten för läkning utan större amputation.

Efter läkning av tidigare sår, utvecklade 34% nya sår på samma fot inom observationstiden. Tjugotvå procent av patienter som utvecklade nya sår genomgick en amputation innan de nya såren läkte. Lägre grad av maximal sårskada som förelåg för det tidigare såret, och öppen rekonstruktiv kärlkirurgi, var relaterad till lägre risk för utveckling av nya sår. Patienter med diabetes och fotsår orsakat av nedsatt cirkulation hade en medianöverlevnad på 33 månader.

Sammanfattningsvis visar denna avhandling att hos patienter med diabetes och fotsår orsakat av nedsatt cirkulation är sannolikheten för sårhäkning starkt relaterad till samsjuklighet, graden av sårskada, och svårighetsgraden av perifer kärlsjukdom. Resultatet visar också att fotsår orsakat av nedsatt cirkulation hos patienter med diabetes som inte är tillgängliga för revaskularisering kan läka utan större amputation. Vid nedsatt perifer cirkulation är, förutom revaskularisering, tiden till revaskularisering också viktig för sårhäkning utan större amputation. Efter

sårläkning, har dessa patienter hög risk för att utveckla nya sår. Graden av tidigare sårskada och rekonstruktiv kärlkirurgi påverkade risken för utveckling av nya sår.

# Acknowledgements

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I wish to express my sincere gratitude to everyone who has helped me by contributing to this work. I would especially like to thank:

Every patient at the diabetic foot clinic, who taught me to keep up my enthusiasm and hope until the end.

Associate Professor **Karl-Fredrik Eriksson**, my supervisor, for his continued help, guidance and invaluable support.

Associate Professor **Jan Apelqvist**, my co-supervisor, for introducing me to the world of the diabetic foot, sharing valuable knowledge, endless support and patience.

Professor **Leif Groop**, my co-supervisor, for all his support and help since my start at the endocrine clinic.

My co-authors, **Jan Larsson, Johan Thörne, Per Nyberg and Magnus Löndahl** for your valuable comments, discussions, contributions and support.

The diabetic foot team at Malmö and Lund **Lena Bengtsson, Marita Jonsson, Marie Cederberg, Lena Olsson, Nicole Berglund, Anne-Charlotte Olsson, Gunilla Larsson, Åsa Asmundsson, Mirja Ruonakoski Ley and Irene Dupros** for making my journey at the foot clinic joyful. I've learned a lot from you.

**Anders Frid**, my clinical mentor, for always taking time to help, collaboration and valuable discussions.

**Eero Lindholm**, for your support; working with you is both constructive and fun.

All my colleagues at the clinic in **Malmö** and **Lund** for your support and teaching me endocrinology.

**Nael Shaat** for your friendship, support and good advices.

**Magdalena Gershater** for your support and encouragement.

All **nurses, assistant nurses, and secretaries** at the endocrinology department for making the clinic feel like home.

All my teachers and colleagues in Benghazi, Helsingborg and Malmö, for teaching me medicine, support and friendship.

My dear sister **Hanan** and her family, my brother **Mohammad** and my dear father-in-law **Muftah Madi**, for being in my life.

Last, but most important, my gratitude to my beloved wife **Nadia**, and my children **Nour, Nada, Abdelmalek and Yosef** for your endless love, joy, understanding, support and patience.

# References

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1. International Working Group on the Diabetic Foot. International consensus on the diabetic foot and practical guidelines on the management and the prevention of the diabetic foot. Amsterdam: International Working Group on the Diabetic Foot; 2011. [DVD].
2. Larsson J, Apelqvist J. Towards less amputations in diabetic patients. Incidence, causes, cost, treatment, and prevention--a review. *Acta orthopaedica Scandinavica*. 1995;66(2):181-92.
3. Nather A, Wong KL. Distal amputations for the diabetic foot. *Diabetic foot & ankle*. 2013;4. doi: 10.3402/dfa.v4i0.21288.
4. Wagner FW Jr. The dysvascular foot: a system for diagnosis and treatment. *Foot Ankle*. 1981;2(2):64-122.
5. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2014;37 Suppl 1:S81-90.
6. International Diabetes Federation. *IDF Diabetes Atlas*, 6th edn. Brussels, Belgium: International Diabetes Federation, 2013. <http://www.idf.org/diabetesatlas>.
7. Dyck PJ, Kratz KM, Karnes JL, Litchy WJ, *et al*. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. *Neurology*. 1993;43(4):817-24.
8. Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, *et al*. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care*. 2010;33(10):2285-93.
9. Davies M, Brophy S, Williams R, Taylor A. The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes. *Diabetes Care*. 2006;29(7):1518-22.
10. Tesfaye S, Stevens LK, Stephenson JM, Fuller JH, *et al*. Prevalence of diabetic peripheral neuropathy and its relation to glycaemic control and potential risk factors: the EURODIAB IDDM Complications Study. *Diabetologia*. 1996;39(11):1377-84.
11. Young MJ, Boulton AJ, MacLeod AF, Williams DR, *et al*. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. *Diabetologia*. 1993;36(2):150-4.

12. Tesfaye S, Chaturvedi N, Eaton SE, Ward JD, *et al.* Vascular risk factors and diabetic neuropathy. *The New England journal of medicine.* 2005;352(4):341-50.
13. Abbott CA, Vileikyte L, Williamson S, Carrington AL, *et al.* Multicenter study of the incidence of and predictive risk factors for diabetic neuropathic foot ulceration. *Diabetes Care.* 1998;21(7):1071-5.
14. Boulton AJ. The diabetic foot: grand overview, epidemiology and pathogenesis. *Diabetes Metab Res Rev.* 2008;24 Suppl 1:S3-6.
15. Boulton AJ. Diabetic neuropathy: is pain God's greatest gift to mankind? *Seminars in vascular surgery.* 2012;25(2):61-5.
16. Tegner R. The effect of skin temperature on vibratory sensitivity in polyneuropathy. *Journal of neurology, neurosurgery, and psychiatry.* 1985;48(2):176-8.
17. Ward JD, Boulton AJ, Simms JM, Sandler DA, *et al.* Venous distension in the diabetic neuropathic foot (physical sign of arteriovenous shunting). *Journal of the Royal Society of Medicine.* 1983;76(12):1011-4.
18. U.S. Renal Data System, *USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2013.
19. American Diabetes Association. Standards of medical care in diabetes--2014. *Diabetes Care.* 2014;37 Suppl 1:S14-80.
20. Levey AS, Coresh J, Balk E, Kausz AT, *et al.* National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Annals of internal medicine.* 2003;139(2):137-47.
21. Gall MA, Hougaard P, Borch-Johnsen K, Parving HH. Risk factors for development of incipient and overt diabetic nephropathy in patients with non-insulin dependent diabetes mellitus: prospective, observational study. *BMJ.* 1997;314(7083):783-8.
22. Chadban S, Howell M, Twigg S, Thomas M, *et al.* The CARI guidelines. Assessment of kidney function in type 2 diabetes. *Nephrology.* 2010;15 Suppl 1:S146-61.
23. Ravid M, Brosh D, Ravid-Safran D, Levy Z, *et al.* Main risk factors for nephropathy in type 2 diabetes mellitus are plasma cholesterol levels, mean blood pressure, and hyperglycemia. *Arch Intern Med.* 1998;158(9):998-1004.
24. Sawicki PT, Didjurgeit U, Muhlhauser I, Bender R, *et al.* Smoking is associated with progression of diabetic nephropathy. *Diabetes Care.* 1994;17(2):126-31.
25. Adler AI, Stevens RJ, Manley SE, Bilous RW, *et al.* Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney international.* 2003;63(1):225-32.



26. Ninomiya T, Perkovic V, de Galan BE, Zoungas S, *et al.* Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. *Journal of the American Society of Nephrology : JASN.* 2009;20(8):1813-21.
27. Groop PH, Thomas MC, Moran JL, Waden J, *et al.* The presence and severity of chronic kidney disease predicts all-cause mortality in type 1 diabetes. *Diabetes.* 2009;58(7):1651-8.
28. Lavery LA, Hunt NA, Ndip A, Lavery DC, *et al.* Impact of chronic kidney disease on survival after amputation in individuals with diabetes. *Diabetes Care.* 2010;33(11):2365-9.
29. Bilous R. Microvascular disease: what does the UKPDS tell us about diabetic nephropathy? *Diabet Med.* 2008;25 Suppl 2:25-9.
30. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *The New England journal of medicine.* 2008;358(6):580-91.
31. Zoungas S, de Galan BE, Ninomiya T, Grobbee D, *et al.* Combined effects of routine blood pressure lowering and intensive glucose control on macrovascular and microvascular outcomes in patients with type 2 diabetes: New results from the ADVANCE trial. *Diabetes Care.* 2009;32(11):2068-74.
32. Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, *et al.* The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *The New England journal of medicine.* 2001;345(12):870-8.
33. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, *et al.* Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *The New England journal of medicine.* 2001;345(12):851-60.
34. Gershater MA, Londahl M, Nyberg P, Larsson J, *et al.* Complexity of factors related to outcome of neuropathic and neuroischaemic/ischaemic diabetic foot ulcers: a cohort study. *Diabetologia.* 2009;52(3):398-407.
35. Prompers L, Schaper N, Apelqvist J, Edmonds M, *et al.* Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. *The EURODIALE Study. Diabetologia.* 2008;51(5):747-55.
36. Eggers PW, Gohdes D, Pugh J. Nontraumatic lower extremity amputations in the Medicare end-stage renal disease population. *Kidney international.* 1999;56(4):1524-33.
37. Hinchliffe RJ, Andros G, Apelqvist J, Bakker K, *et al.* A systematic review of the effectiveness of revascularization of the ulcerated foot in patients with diabetes and peripheral arterial disease. *Diabetes Metab Res Rev.* 2012;28 Suppl 1:179-217.
38. Joussen AM, Smyth N, Niessen C. Pathophysiology of diabetic macular edema. *Developments in ophthalmology.* 2007;39:1-12.

39. Brown MM, Brown GC, Sharma S, Shah G. Utility values and diabetic retinopathy. *American journal of ophthalmology*. 1999;128(3):324-30.
40. Klein R. The epidemiology of diabetic retinopathy: findings from the Wisconsin Epidemiologic Study of Diabetic Retinopathy. *International ophthalmology clinics*. 1987;27(4):230-8.
41. Klein R, Knudtson MD, Lee KE, Gangnon R, *et al*. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XXII the twenty-five-year progression of retinopathy in persons with type 1 diabetes. *Ophthalmology*. 2008;115(11):1859-68.
42. Klein R. Hyperglycemia and microvascular and macrovascular disease in diabetes. *Diabetes Care*. 1995;18(2):258-68.
43. Estacio RO, McFarling E, Biggerstaff S, Jeffers BW, *et al*. Overt albuminuria predicts diabetic retinopathy in Hispanics with NIDDM. *American journal of kidney diseases*. 1998;31(6):947-53.
44. Leske MC, Wu SY, Hennis A, Hyman L, *et al*. Hyperglycemia, blood pressure, and the 9-year incidence of diabetic retinopathy: the Barbados Eye Studies. *Ophthalmology*. 2005;112(5):799-805.
45. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *The New England journal of medicine*. 1993;329(14):977-86.
46. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352(9131):854-65.
47. Monteiro-Soares M, Boyko EJ, Ribeiro J, Ribeiro I, *et al*. Predictive factors for diabetic foot ulceration: a systematic review. *Diabetes Metab Res Rev*. 2012;28(7):574-600.
48. Bruun C, Siersma V, Guassora AD, Holstein P, *et al*. Amputations and foot ulcers in patients newly diagnosed with type 2 diabetes mellitus and observed for 19 years. The role of age, gender and co-morbidity. *Diabet Med*. 2013;30(8):964-72.
49. Moss SE, Klein R, Klein BE. The 14-year incidence of lower-extremity amputations in a diabetic population. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Diabetes Care*. 1999;22(6):951-9.
50. Centers for Disease Control and Prevention. National diabetes fact sheet. Available at: <http://www.cdc.gov/diabetes/pubs/statsreport14.htm>. 2014.
51. Holman RR, Paul SK, Bethel MA, Matthews DR, *et al*. 10-year follow-up of intensive glucose control in type 2 diabetes. *The New England journal of medicine*. 2008;359(15):1577-89.
52. Nathan DM, Cleary PA, Backlund JY, Genuth SM, *et al*. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *The New England journal of medicine*. 2005;353(25):2643-53.

53. The Diabetes Control and Complications Trial (DCCT) Research Group. Effect of intensive diabetes management on macrovascular events and risk factors in the Diabetes Control and Complications Trial. *The American journal of cardiology*. 1995;75(14):894-903.
54. Pinto A, Tuttolomondo A, Di Raimondo D, Fernandez P, *et al*. Cardiovascular risk profile and morbidity in subjects affected by type 2 diabetes mellitus with and without diabetic foot. *Metabolism: clinical and experimental*. 2008;57(5):676-82.
55. Heald CL, Fowkes FG, Murray GD, Price JF. Risk of mortality and cardiovascular disease associated with the ankle-brachial index: Systematic review. *Atherosclerosis*. 2006;189(1):61-9.
56. Leng GC, Fowkes FG, Lee AJ, Dunbar J, *et al*. Use of ankle brachial pressure index to predict cardiovascular events and death: a cohort study. *BMJ (Clinical research ed)*. 1996;313(7070):1440-4.
57. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352(9131):837-53.
58. Pinto A, Tuttolomondo A, Di Raimondo D, La Placa S, *et al*. Ischemic stroke in patients with diabetic foot. *Int Angiol*. 2007;26(3):266-9.
59. Schaper NC, Andros G, Apelqvist J, Bakker K, *et al*. Diagnosis and treatment of peripheral arterial disease in diabetic patients with a foot ulcer. A progress report of the International Working Group on the Diabetic Foot. *Diabetes Metab Res Rev*. 2012;28 Suppl 1:218-24.
60. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. *JAMA : the journal of the American Medical Association*. 2005;293(2):217-28.
61. Pecoraro RE, Reiber GE, Burgess EM. Pathways to diabetic limb amputation. Basis for prevention. *Diabetes Care*. 1990;13(5):513-21.
62. van Acker K, Leger P, Hartemann A, Chawla A, *et al*. Burden of diabetic foot disorders, guidelines for management, and disparities in implementation in Europe: a systematic literature review. *Diabetes Metab Res Rev*. 2014 Jan 27. doi: 10.1002/dmrr.2523. [Epub ahead of print].
63. Edmonds M. Experience in a multi-disciplinary diabetic foot clinic. In: Boulton AJM, Connor H, Ward JD, editors. *The Foot in Diabetes*. 1st ed. Chichester, UK: Wiley; 1987:121-33.
64. Ndip A, Jude EB. Emerging evidence for neuroischemic diabetic foot ulcers: model of care and how to adapt practice. *Int J Low Extrem Wounds*. 2009;8(2):82-94.
65. Oyibo SO, Jude EB, Voyatzoglou D, Boulton AJM. Clinical characteristics of patients with diabetic foot problems: changing patterns of foot ulcer presentation. *Pract Diabet Int*. 2002;19(1):10-2.

66. Abbott CA, Carrington AL, Ashe H, Bath S, *et al.* The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. *Diabet Med.* 2002;19(5):377-84.
67. Boyko EJ, Ahroni JH, Stensel V, Forsberg RC, *et al.* A prospective study of risk factors for diabetic foot ulcer. The Seattle Diabetic Foot Study. *Diabetes Care.* 1999;22(7):1036-42.
68. Reiber GE, Vileikyte L, Boyko EJ, del Aguila M, *et al.* Causal pathways for incident lower-extremity ulcers in patients with diabetes from two settings. *Diabetes Care.* 1999;22(1):157-62.
69. Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation. *Diabetes Care.* 1998;21(5):855-9.
70. Lavery LA, Armstrong DG, Wunderlich RP, Mohler MJ, *et al.* Risk factors for foot infections in individuals with diabetes. *Diabetes Care.* 2006;29(6):1288-93.
71. The Saint Vincent Declaration on diabetes care and research in Europe. *Acta diabetologica.* 1989;10:143-4.
72. Cavanagh PR, Bus SA. Off-loading the diabetic foot for ulcer prevention and healing. *J Vasc Surg.* 2010;52(3 Suppl):37S-43S.
73. Gibbons GW, Marcaccio EJ Jr., Burgess AM, Pomposelli FB Jr., *et al.* Improved quality of diabetic foot care, 1984 vs 1990. Reduced length of stay and costs, insufficient reimbursement. *Archives of surgery.* 1993;128(5):576-81.
74. Apelqvist J, Larsson J. What is the most effective way to reduce incidence of amputation in the diabetic foot? *Diabetes Metab Res Rev.* 2000;16 Suppl 1:S75-83.
75. Faglia E, Favales F, Aldeghi A, Calia P, *et al.* Change in major amputation rate in a center dedicated to diabetic foot care during the 1980s: prognostic determinants for major amputation. *J Diabetes Complications.* 1998;12(2):96-102.
76. Rubio JA, Aragon-Sanchez J, Jimenez S, Guadalix G, *et al.* Reducing major lower extremity amputations after the introduction of a multidisciplinary team for the diabetic foot. *Int J Low Extrem Wounds.* 2014;13(1):22-6.
77. Dargis V, Pantelejeva O, Jonushaite A, Vileikyte L, *et al.* Benefits of a multidisciplinary approach in the management of recurrent diabetic foot ulceration in Lithuania: a prospective study. *Diabetes Care.* 1999;22(9):1428-31.
78. Edmonds ME, Blundell MP, Morris ME, Thomas EM, *et al.* Improved survival of the diabetic foot: the role of a specialized foot clinic. *The Quarterly journal of medicine.* 1986;60(232):763-71.
79. Apelqvist J. Diagnostics and treatment of the diabetic foot. *Endocrine.* 2012;41(3):384-97.

80. Blume PA, Walters J, Payne W, Ayala J, *et al.* Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial. *Diabetes Care.* 2008;31(4):631-6.
81. Sepulveda G, Espindola M, Maureira M, Sepulveda E, *et al.* [Negative-pressure wound therapy versus standard wound dressing in the treatment of diabetic foot amputation. A randomised controlled trial]. *Cirugia espanola.* 2009;86(3):171-7.
82. Uckay I, Gariani K, Pataky Z, Lipsky BA. Diabetic foot infections: state-of-the-art. *Diabetes, obesity & metabolism.* 2014;16(4):305-16.
83. Apelqvist JA, Lepantalo MJ. The ulcerated leg: when to revascularize. *Diabetes Metab Res Rev.* 2012;28 Suppl 1:30-5.
84. Azuma N, Uchida H, Kokubo T, Koya A, *et al.* Factors influencing wound healing of critical ischaemic foot after bypass surgery: is the angiosome important in selecting bypass target artery? *Eur J Vasc Endovasc Surg.* 2012;43(3):322-8.
85. Kawarada O, Fujihara M, Higashimori A, Yokoi Y, *et al.* Predictors of adverse clinical outcomes after successful infrapopliteal intervention. *Catheterization and cardiovascular interventions.* 2012;80(5):861-71.
86. Malmstedt J, Leander K, Wahlberg E, Karlstrom L, *et al.* Outcome after leg bypass surgery for critical limb ischemia is poor in patients with diabetes: a population-based cohort study. *Diabetes Care.* 2008;31(5):887-92.
87. Uccioli L, Gandini R, Giurato L, Fabiano S, *et al.* Long-term outcomes of diabetic patients with critical limb ischemia followed in a tertiary referral diabetic foot clinic. *Diabetes Care.* 2010;33(5):977-82.
88. Apelqvist J, Agardh CD. The association between clinical risk factors and outcome of diabetic foot ulcers. *Diabetes Res Clin Pract.* 1992;18(1):43-53.
89. Oyibo SO, Jude EB, Tarawneh I, Nguyen HC, *et al.* The effects of ulcer size and site, patient's age, sex and type and duration of diabetes on the outcome of diabetic foot ulcers. *Diabet Med.* 2001;18(2):133-8.
90. Pickwell KM, Siersma VD, Kars M, Holstein PE, *et al.* Diabetic foot disease: impact of ulcer location on ulcer healing. *Diabetes Metab Res Rev.* 2013;29(5):377-83.
91. Resnick HE, Carter EA, Sosenko JM, Henly SJ, *et al.* Incidence of lower-extremity amputation in American Indians: the Strong Heart Study. *Diabetes Care.* 2004;27(8):1885-91.
92. Reiber GE, Pecoraro RE, Koepsell TD. Risk factors for amputation in patients with diabetes mellitus. A case-control study. *Annals of internal medicine.* 1992;117(2):97-105.
93. Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. Diabetic neuropathic foot ulcers: the association of wound size, wound duration, and wound grade on healing. *Diabetes Care.* 2002;25(10):1835-9.
94. Larsson J, Eneroth M, Apelqvist J, Stenstrom A. Sustained reduction in major amputations in diabetic patients: 628 amputations in 461 patients in a

- defined population over a 20-year period. *Acta orthopaedica*. 2008;79(5):665-73.
95. Lepantalo M, Matzke S. Outcome of unreconstructed chronic critical leg ischaemia. *Eur J Vasc Endovasc Surg*. 1996;11(2):153-7.
  96. Marston WA, Davies SW, Armstrong B, Farber MA, *et al*. Natural history of limbs with arterial insufficiency and chronic ulceration treated without revascularization. *J Vasc Surg*. 2006;44(1):108-14.
  97. Apelqvist J, Larsson J, Agardh CD. Long-term prognosis for diabetic patients with foot ulcers. *J Intern Med*. 1993;233(6):485-91.
  98. Faglia E, Favales F, Morabito A. New ulceration, new major amputation, and survival rates in diabetic subjects hospitalized for foot ulceration from 1990 to 1993: a 6.5-year follow-up. *Diabetes Care*. 2001;24(1):78-83.
  99. Otiniano ME, Du X, Ottenbacher K, Black SA, *et al*. Lower extremity amputations in diabetic Mexican American elders: incidence, prevalence and correlates. *J Diabetes Complications*. 2003;17(2):59-65.
  100. Pound N, Chipchase S, Treece K, Game F, *et al*. Ulcer-free survival following management of foot ulcers in diabetes. *Diabet Med*. 2005;22(10):1306-9.
  101. Wolfle KD, Bruijnen H, Loeprecht H, Rumenapf G, *et al*. Graft patency and clinical outcome of femorodistal arterial reconstruction in diabetic and non-diabetic patients: results of a multicentre comparative analysis. *Eur J Vasc Endovasc Surg*. 2003;25(3):229-34.
  102. Faglia E, Clerici G, Scatena A, Caminiti M, *et al*. Effectiveness of combined therapy with angiotensin-converting enzyme inhibitors and statins in reducing mortality in diabetic patients with critical limb ischemia: an observational study. *Diabetes Res Clin Pract*. 2014;103(2):292-7.
  103. Young MJ, McCardle JE, Randall LE, Barclay JI. Improved survival of diabetic foot ulcer patients 1995-2008: possible impact of aggressive cardiovascular risk management. *Diabetes Care*. 2008;31(11):2143-7.
  104. Marrocco CJ, Bush RL. Chapter 1: peripheral arterial disease. In: Lavery LA, Peters EJG, Bush RL, editors. *High Risk Diabetic Foot, Treatment and Prevention: Informa Healthcare*; 2010:1-8.
  105. Meves SH, Diehm C, Berger K, Pittrow D, *et al*. Peripheral arterial disease as an independent predictor for excess stroke morbidity and mortality in primary-care patients: 5-year results of the getABI study. *Cerebrovascular diseases*. 2010;29(6):546-54.
  106. Fowkes FG, Rudan D, Rudan I, Aboyans V, *et al*. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet*. 2013;382(9901):1329-40.
  107. Shah B, Rockman CB, Guo Y, Chesner J, *et al*. Diabetes and Vascular Disease in Different Arterial Territories. *Diabetes Care*. 2014;37(6):1636-42.

108. Newman AB, Siscovick DS, Manolio TA, Polak J, *et al.* Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Cardiovascular Heart Study (CHS) Collaborative Research Group. *Circulation*. 1993;88(3):837-45.
109. Adler AI, Stevens RJ, Neil A, Stratton IM, *et al.* UKPDS 59: hyperglycemia and other potentially modifiable risk factors for peripheral vascular disease in type 2 diabetes. *Diabetes Care*. 2002;25(5):894-9.
110. Jeffcoate WJ, Chipchase SY, Ince P, Game FL. Assessing the outcome of the management of diabetic foot ulcers using ulcer-related and person-related measures. *Diabetes Care*. 2006;29(8):1784-7.
111. Faglia E, Favales F, Quarantiello A, Calia P, *et al.* Angiographic evaluation of peripheral arterial occlusive disease and its role as a prognostic determinant for major amputation in diabetic subjects with foot ulcers. *Diabetes Care*. 1998;21(4):625-30.
112. Claesson K, Kolbel T, Acosta S. Role of endovascular intervention in patients with diabetic foot ulcer and concomitant peripheral arterial disease. *Int Angiol*. 2011;30(4):349-58.
113. Graziani L, Silvestro A, Bertone V, Manara E, *et al.* Vascular involvement in diabetic subjects with ischemic foot ulcer: a new morphologic categorization of disease severity. *Eur J Vasc Endovasc Surg*. 2007;33(4):453-60.
114. Jude EB, Oyibo SO, Chalmers N, Boulton AJ. Peripheral arterial disease in diabetic and nondiabetic patients: a comparison of severity and outcome. *Diabetes Care*. 2001;24(8):1433-7.
115. De Vivo S, Palmer-Kazen U, Kalin B, Wahlberg E. Risk factors for poor collateral development in claudication. *Vascular and endovascular surgery*. 2005;39(6):519-24.
116. Young MJ, Adams JE, Anderson GF, Boulton AJ, *et al.* Medial arterial calcification in the feet of diabetic patients and matched non-diabetic control subjects. *Diabetologia*. 1993;36(7):615-21.
117. Everhart JE, Pettitt DJ, Knowler WC, Rose FA, *et al.* Medial arterial calcification and its association with mortality and complications of diabetes. *Diabetologia*. 1988;31(1):16-23.
118. Jorreskog G. Why critical limb ischemia criteria are not applicable to diabetic foot and what the consequences are. *Scandinavian journal of surgery*. 2012;101(2):114-8.
119. Chao CY, Cheing GL. Microvascular dysfunction in diabetic foot disease and ulceration. *Diabetes Metab Res Rev*. 2009;25(7):604-14.
120. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, *et al.* Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg*. 2007;45 Suppl S:S5-67.
121. Willigendael EM, Teijink JA, Bartelink ML, Kuiken BW, *et al.* Influence of smoking on incidence and prevalence of peripheral arterial disease. *J Vasc Surg*. 2004;40(6):1158-65.

122. Hooi JD, Kester AD, Stoffers HE, Overdijk MM, *et al.* Incidence of and risk factors for asymptomatic peripheral arterial occlusive disease: a longitudinal study. *American journal of epidemiology.* 2001;153(7):666-72.
123. Fowkes FG, Housley E, Cawood EH, Macintyre CC, *et al.* Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. *Int J Epidemiol.* 1991;20(2):384-92.
124. Anderson JJ, Boone J, Hansen M, Spencer L, *et al.* A comparison of diabetic smokers and non-smokers who undergo lower extremity amputation: a retrospective review of 112 patients. *Diabetic foot & ankle.* 2012;3. doi: 10.3402/dfa.v3i0.19178.
125. McDaniel MD, Cronenwett JL. Basic data related to the natural history of intermittent claudication. *Ann Vasc Surg.* 1989;3(3):273-7.
126. Selvin E, Marinopoulos S, Berkenblit G, Rami T, *et al.* Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Annals of internal medicine.* 2004;141(6):421-31.
127. Muntner P, Wildman RP, Reynolds K, Desalvo KB, *et al.* Relationship between HbA1c level and peripheral arterial disease. *Diabetes Care.* 2005;28(8):1981-7.
128. Kallio M, Forsblom C, Groop PH, Groop L, *et al.* Development of new peripheral arterial occlusive disease in patients with type 2 diabetes during a mean follow-up of 11 years. *Diabetes Care.* 2003;26(4):1241-5.
129. Zander E, Heinke P, Reindel J, Kohnert KD, *et al.* Peripheral arterial disease in diabetes mellitus type 1 and type 2: are there different risk factors? *VASA.* 2002;31(4):249-54.
130. Smith I, Franks PJ, Greenhalgh RM, Poulter NR, *et al.* The influence of smoking cessation and hypertriglyceridaemia on the progression of peripheral arterial disease and the onset of critical ischaemia. *Eur J Vasc Endovasc Surg.* 1996;11(4):402-8.
131. Meijer WT, Grobbee DE, Hunink MG, Hofman A, *et al.* Determinants of peripheral arterial disease in the elderly: the Rotterdam study. *Arch Intern Med.* 2000;160(19):2934-8.
132. Murabito JM, D'Agostino RB, Silbershatz H, Wilson WF. Intermittent claudication. A risk profile from The Framingham Heart Study. *Circulation.* 1997;96(1):44-9.
133. Jensen SA, Vatten LJ, Romundstad PR, Myhre HO. The prevalence of intermittent claudication. Sex-related differences have been eliminated. *Eur J Vasc Endovasc Surg.* 2003;25(3):209-12.
134. Kullo IJ, Bailey KR, Kardia SL, Mosley TH Jr., *et al.* Ethnic differences in peripheral arterial disease in the NHLBI Genetic Epidemiology Network of Arteriopathy (GENOA) study. *Vascular medicine.* 2003;8(4):237-42.
135. Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen,



- homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. 2001;285(19):2481-5.
136. Smith FB, Lee AJ, Hau CM, Rumley A, *et al.* Plasma fibrinogen, haemostatic factors and prediction of peripheral arterial disease in the Edinburgh Artery Study. *Blood coagulation & fibrinolysis.* 2000;11(1):43-50.
  137. Sigvant B, Wiberg-Hedman K, Bergqvist D, Rolandsson O, *et al.* Risk factor profiles and use of cardiovascular drug prevention in women and men with peripheral arterial disease. *European journal of cardiovascular prevention and rehabilitation.* 2009;16(1):39-46.
  138. Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, *et al.* Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA.* 2001;286(11):1317-24.
  139. McDermott MM, Greenland P, Liu K, Guralnik JM, *et al.* The ankle brachial index is associated with leg function and physical activity: the Walking and Leg Circulation Study. *Annals of internal medicine.* 2002;136(12):873-83.
  140. Kannel WB. Risk factors for atherosclerotic cardiovascular outcomes in different arterial territories. *Journal of cardiovascular risk.* 1994;1(4):333-9.
  141. Schaper NC, Andros G, Apelqvist J, Bakker K, *et al.* Specific guidelines for the diagnosis and treatment of peripheral arterial disease in a patient with diabetes and ulceration of the foot 2011. *Diabetes Metab Res Rev.* 2012;28 Suppl 1:236-7.
  142. Bakker K, Apelqvist J, Schaper NC, International Working Group on Diabetic Foot Editorial B. Practical guidelines on the management and prevention of the diabetic foot 2011. *Diabetes Metab Res Rev.* 2012;28 Suppl 1:225-31.
  143. American Diabetes Association. Peripheral arterial disease in people with diabetes. *Diabetes Care.* 2003;26(12):3333-41.
  144. Ankle Brachial Index Collaboration, Fowkes FG, Murray GD, Butcher I, *et al.* Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA.* 2008;300(2):197-208.
  145. Cao P, Eckstein HH, De Rango P, Setacci C, *et al.* Chapter II: Diagnostic methods. *Eur J Vasc Endovasc Surg.* 2011;42 Suppl 2:S13-32.
  146. Fife CE, Smart DR, Sheffield PJ, Hopf HW, *et al.* Transcutaneous oximetry in clinical practice: consensus statements from an expert panel based on evidence. *Undersea & hyperbaric medicine.* 2009;36(1):43-53.
  147. Padberg FT, Back TL, Thompson PN, Hobson RW 2nd. Transcutaneous oxygen (TcPO<sub>2</sub>) estimates probability of healing in the ischemic extremity. *The Journal of surgical research.* 1996;60(2):365-9.
  148. Arsenault KA, Al-Otaibi A, Devereaux PJ, Thorlund K, *et al.* The use of transcutaneous oximetry to predict healing complications of lower limb

- amputations: a systematic review and meta-analysis. *Eur J Vasc Endovasc Surg.* 2012;43(3):329-36.
149. Dooley J, Schirmer J, Slade B, Folden B. Use of transcutaneous pressure of oxygen in the evaluation of edematous wounds. *Undersea & hyperbaric medicine.* 1996;23(3):167-74.
  150. Collins R, Burch J, Cranny G, Aguiar-Ibanez R, *et al.* Duplex ultrasonography, magnetic resonance angiography, and computed tomography angiography for diagnosis and assessment of symptomatic, lower limb peripheral arterial disease: systematic review. *BMJ.* 2007;334(7606):1257.
  151. Met R, Bipat S, Legemate DA, Reekers JA, *et al.* Diagnostic performance of computed tomography angiography in peripheral arterial disease: a systematic review and meta-analysis. *JAMA.* 2009;301(4):415-24.
  152. Gregg EW, Li Y, Wang J, Burrows NR, *et al.* Changes in diabetes-related complications in the United States, 1990-2010. *The New England journal of medicine.* 2014;370(16):1514-23.
  153. Rooke TW, Hirsch AT, Misra S, Sidawy AN, *et al.* Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology.* 2013;61(14):1555-70.
  154. Norgren L. Pharmacotherapy for critical limb ischaemia. *Diabetes Metab Res Rev.* 2000;16 Suppl 1:S37-41.
  155. Selvarajah S, Black JH, 3rd, Malas MB, Lum YW, *et al.* Preoperative smoking is associated with early graft failure after infrainguinal bypass surgery. *J Vasc Surg.* 2014;59(5):1308-14.
  156. Ahimastos AA, Walker PJ, Askew C, Leicht A, *et al.* Effect of ramipril on walking times and quality of life among patients with peripheral artery disease and intermittent claudication: a randomized controlled trial. *JAMA.* 2013;309(5):453-60.
  157. Ruffolo AJ, Romano M, Ciapponi A. Prostanoids for critical limb ischaemia. *The Cochrane database of systematic reviews.* 2010(1):CD006544.
  158. ADVANCE Collaboration Group, Patel A, MacMahon S, Chalmers J, *et al.* Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *The New England journal of medicine.* 2008;358(24):2560-72.
  159. Hemmingsen B, Lund SS, Gluud C, Vaag A, *et al.* Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. *The Cochrane database of systematic reviews.* 2013;11:CD008143.
  160. Rathsmann B, Jensen-Urstad K, Nystrom T. Intensified insulin treatment is associated with improvement in skin microcirculation and ischaemic foot

- ulcer in patients with type 1 diabetes mellitus: a long-term follow-up study. *Diabetologia*. 2014;57(8):1703-10.
161. Antithrombotic Trialist's Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002;324(7329):71-86.
  162. Poredos P, Jezovnik MK. Antiplatelet and antithrombotic treatment of patients with peripheral arterial disease. *Int Angiol*. 2010;29(1):20-6.
  163. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348(9038):1329-39.
  164. Aung PP, Maxwell HG, Jepson RG, Price JF, *et al*. Lipid-lowering for peripheral arterial disease of the lower limb. *The Cochrane database of systematic reviews*. 2007(4):CD000123.
  165. Margolis DJ, Gupta J, Hoffstad O, Papdopoulos M, *et al*. Lack of effectiveness of hyperbaric oxygen therapy for the treatment of diabetic foot ulcer and the prevention of amputation: a cohort study. *Diabetes Care*. 2013;36(7):1961-6.
  166. Abidia A, Laden G, Kuhan G, Johnson BF, *et al*. The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. *Eur J Vasc Endovasc Surg*. 2003;25(6):513-8.
  167. Londahl M, Katzman P, Nilsson A, Hammarlund C. Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. *Diabetes Care*. 2010;33(5):998-1003.
  168. Kranke P, Bennett MH, Martyn-St James M, Schnabel A, *et al*. Hyperbaric oxygen therapy for chronic wounds. *The Cochrane database of systematic reviews*. 2012;4:CD004123.
  169. Stoekenbroek RM, Santema TB, Legemate DA, Ubbink DT, *et al*. Hyperbaric Oxygen for the Treatment of Diabetic Foot Ulcers: A Systematic Review. *Eur J Vasc Endovasc Surg*. 2014; 47(6):647-55.
  170. Biancari F, Salenius JP, Heikkinen M, Luther M, *et al*. Risk-scoring method for prediction of 30-day postoperative outcome after infrainguinal surgical revascularization for critical lower-limb ischemia: a Finnvasc registry study. *World J Surg*. 2007;31(1):217-25; discussion 26-7.
  171. Jacqueminet S, Hartemann-Heurtier A, Izzillo R, Cluzel P, *et al*. Percutaneous transluminal angioplasty in severe diabetic foot ischemia: outcomes and prognostic factors. *Diabetes Metab*. 2005;31(4 Pt 1):370-5.
  172. Zhu YQ, Zhao JG, Liu F, Wang JB, *et al*. Subintimal angioplasty for below-the-ankle arterial occlusions in diabetic patients with chronic critical limb ischemia. *J Endovasc Ther*. 2009;16(5):604-12.
  173. Setacci C, de Donato G, Teraa M, Moll FL, *et al*. Chapter IV: Treatment of critical limb ischaemia. *Eur J Vasc Endovasc Surg*. 2011;42 Suppl 2:S43-59.

174. Adam DJ, Beard JD, Cleveland T, Bell J, *et al.* Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. *Lancet.* 2005;366(9501):1925-34.
175. Conrad MF, Kang J, Cambria RP, Brewster DC, *et al.* Infrapopliteal balloon angioplasty for the treatment of chronic occlusive disease. *J Vasc Surg.* 2009;50(4):799-805 e4.
176. Mills JL, Sr. Open bypass and endoluminal therapy: complementary techniques for revascularization in diabetic patients with critical limb ischaemia. *Diabetes Metab Res Rev.* 2008;24 Suppl 1:S34-9.
177. Laird JR. Limitations of percutaneous transluminal angioplasty and stenting for the treatment of disease of the superficial femoral and popliteal arteries. *J Endovasc Ther.* 2006;13 Suppl 2:II30-40.
178. Alexandrescu V, Hubermont G, Philips Y, Guillaumie B, *et al.* Combined primary subintimal and endoluminal angioplasty for ischaemic inferior-limb ulcers in diabetic patients: 5-year practice in a multidisciplinary 'diabetic-foot' service. *Eur J Vasc Endovasc Surg.* 2009;37(4):448-56.
179. Bradbury AW, Adam DJ, Bell J, Forbes JF, *et al.* Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: Analysis of amputation free and overall survival by treatment received. *J Vasc Surg.* 2010;51(5 Suppl):18S-31S.
180. Bradbury AW, Adam DJ, Bell J, Forbes JF, *et al.* Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: An intention-to-treat analysis of amputation-free and overall survival in patients randomized to a bypass surgery-first or a balloon angioplasty-first revascularization strategy. *J Vasc Surg.* 2010;51(5 Suppl):5S-17S.
181. Fontaine R, Kim M, Kieny R. [Surgical treatment of peripheral circulation disorders.]. *Helv Chir Acta.* 1954;21(5-6):499-533.
182. Larsson J, Agardh CD, Apelqvist J, Stenstrom A. Long-term prognosis after healed amputation in patients with diabetes. *Clin Orthop Relat Res.* 1998(350):149-58.
183. Colwell JA, Bingham SF, Abaira C, Anderson JW, *et al.* V.A. Cooperative Study on antiplatelet agents in diabetic patients after amputation for gangrene: III. Definitions and review of design and baseline characteristics. *Horm Metab Res Suppl.* 1985;15:69-73.
184. Cannon JA. Intermittent Claudication. What It Is and Isn't. *Calif Med.* 1965;102:301-5.
185. Apelqvist J, Castenfors J, Larsson J, Stenstrom A, *et al.* Prognostic value of systolic ankle and toe blood pressure levels in outcome of diabetic foot ulcer. *Diabetes Care.* 1989;12(6):373-8.
186. Eneroth M, Larsson J, Oscarsson C, Apelqvist J. Nutritional supplementation for diabetic foot ulcers: the first RCT. *J Wound Care.* 2004;13(6):230-4.

187. Eneroth M, Larsson J, Apelqvist J. Deep foot infections in patients with diabetes and foot ulcer: an entity with different characteristics, treatments, and prognosis. *J Diabetes Complications*. 1999;13(5-6):254-63.
188. Armstrong DG, Lavery LA, Vela SA, Quebedeaux TL, *et al*. Choosing a practical screening instrument to identify patients at risk for diabetic foot ulceration. *Arch Intern Med*. 1998;158(3):289-92.
189. Apelqvist J, Torffvit O, Agardh CD. The effect of the non-ionic contrast medium iohexol on glomerular and tubular function in diabetic patients. *Diabet Med*. 1996;13(5):487-92.
190. Kalani M, Apelqvist J, Blomback M, Brismar K, *et al*. Effect of dalteparin on healing of chronic foot ulcers in diabetic patients with peripheral arterial occlusive disease: a prospective, randomized, double-blind, placebo-controlled study. *Diabetes Care*. 2003;26(9):2575-80.
191. Apelqvist J, Castenfors J, Larsson J, Stenstrom A, *et al*. Ketanserin in the treatment of diabetic foot ulcer with severe peripheral vascular disease. *Int Angiol*. 1990;9(2):120-4.
192. Prompers L, Huijberts M, Apelqvist J, Jude E, *et al*. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. *Diabetologia*. 2007;50(1):18-25.
193. DeRubertis BG, Pierce M, Ryer EJ, Trocciola S, *et al*. Reduced primary patency rate in diabetic patients after percutaneous intervention results from more frequent presentation with limb-threatening ischemia. *J Vasc Surg*. 2008;47(1):101-8.
194. Londahl M, Katzman P, Fredholm O, Nilsson A, *et al*. Is chronic diabetic foot ulcer an indicator of cardiac disease? *J Wound Care*. 2008;17(1):12-6.
195. Yang Y, Ostbye T, Tan SB, Abdul Salam ZH, *et al*. Risk factors for lower extremity amputation among patients with diabetes in Singapore. *J Diabetes Complications*. 2011;25(6):382-6.
196. Abbas ZG, Lutale JK, Game FL, Jeffcoate WJ. Comparison of four systems of classification of diabetic foot ulcers in Tanzania. *Diabet Med*. 2008;25(2):134-7.
197. Oyibo SO, Jude EB, Tarawneh I, Nguyen HC, *et al*. A comparison of two diabetic foot ulcer classification systems: the Wagner and the University of Texas wound classification systems. *Diabetes Care*. 2001;24(1):84-8.
198. Karthikesalingam A, Holt PJ, Moxey P, Jones KG, *et al*. A systematic review of scoring systems for diabetic foot ulcers. *Diabet Med*. 2010;27(5):544-9.
199. Monteiro-Soares M, Martins-Mendes D, Vaz-Carneiro A, Sampaio S, *et al*. Classification systems for lower extremity amputation prediction in subjects with active diabetic foot ulcer: a systematic review and meta-analysis. *Diabetes Metab Res Rev*. 2014 Feb 12. doi: 10.1002/dmrr.2535. [Epub ahead of print].

200. Faglia E, Dalla Paola L, Clerici G, Clerissi J, *et al.* Peripheral angioplasty as the first-choice revascularization procedure in diabetic patients with critical limb ischemia: prospective study of 993 consecutive patients hospitalized and followed between 1999 and 2003. *Eur J Vasc Endovasc Surg.* 2005;29(6):620-7.
201. Taylor LM Jr., Edwards JM, Brant B, Phinney ES, *et al.* Autogenous reversed vein bypass for lower extremity ischemia in patients with absent or inadequate greater saphenous vein. *Am J Surg.* 1987;153(5):505-10.
202. Lepantalo M, Apelqvist J, Setacci C, Ricco JB, *et al.* Chapter V: Diabetic foot. *Eur J Vasc Endovasc Surg.* 2011;42 Suppl 2:S60-74.
203. Faglia E, Clerici G, Caminiti M, Quarantiello A, *et al.* The role of early surgical debridement and revascularization in patients with diabetes and deep foot space abscess: retrospective review of 106 patients with diabetes. *The Journal of foot and ankle surgery.* 2006;45(4):220-6.
204. Macfarlane RM, Jeffcoate WJ. Factors contributing to the presentation of diabetic foot ulcers. *Diabet Med.* 1997;14(10):867-70.
205. Apelqvist J. The foot in perspective. *Diabetes Metab Res Rev.* 2008;24 Suppl 1:S110-5.
206. Mills JL, Beckett WC, Taylor SM. The diabetic foot: consequences of delayed treatment and referral. *Southern medical journal.* 1991;84(8):970-4.
207. Del Aguila MA, Reiber GE, Koepsell TD. How does provider and patient awareness of high-risk status for lower-extremity amputation influence foot-care practice? *Diabetes Care.* 1994;17(9):1050-4.
208. Faglia E, Clerici G, Clerissi J, Gabrielli L, *et al.* Long-term prognosis of diabetic patients with critical limb ischemia: a population-based cohort study. *Diabetes Care.* 2009;32(5):822-7.
209. Morbach S, Furchert H, Groblichhoff U, Hoffmeier H, *et al.* Long-term prognosis of diabetic foot patients and their limbs: amputation and death over the course of a decade. *Diabetes Care.* 2012;35(10):2021-7.
210. Chu YJ, Li XW, Wang PH, Xu J, *et al.* Clinical outcomes of toe amputation in patients with type 2 diabetes in Tianjin, China. *International wound journal.* 2014 Mar 14. doi: 10.1111/iwj.12249. [Epub ahead of print].
211. Scatena A, Petruzzi P, Ferrari M, Rizzo L, *et al.* Outcomes of three years of teamwork on critical limb ischemia in patients with diabetes and foot lesions. *Int J Low Extrem Wounds.* 2012;11(2):113-9.
212. Iida O, Soga Y, Hirano K, Kawasaki D, *et al.* Long-term results of direct and indirect endovascular revascularization based on the angiosome concept in patients with critical limb ischemia presenting with isolated below-the-knee lesions. *J Vasc Surg.* 2012;55(2):363-70 e5.
213. Neville RF, Attinger CE, Bulan EJ, Ducic I, *et al.* Revascularization of a specific angiosome for limb salvage: does the target artery matter? *Ann Vasc Surg.* 2009;23(3):367-73.
214. Varela C, Acin F, de Haro J, Bleda S, *et al.* The role of foot collateral vessels on ulcer healing and limb salvage after successful endovascular and

- surgical distal procedures according to an angiosome model. *Vascular and endovascular surgery*. 2010;44(8):654-60.
215. Neville RF, Sidawy AN. Surgical bypass: when is it best and do angiosomes play a role? *Seminars in vascular surgery*. 2012;25(2):102-7.
  216. Conte MS. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) and the (hoped for) dawn of evidence-based treatment for advanced limb ischemia. *J Vasc Surg*. 2010;51(5 Suppl):69S-75S.
  217. Skoutas D, Papanas N, Georgiadis GS, Zervas V, *et al*. Risk factors for ipsilateral reamputation in patients with diabetic foot lesions. *Int J Low Extrem Wounds*. 2009;8(2):69-74.
  218. Faglia E, Clerici G, Clerissi J, Gabrielli L, *et al*. Early and five-year amputation and survival rate of diabetic patients with critical limb ischemia: data of a cohort study of 564 patients. *Eur J Vasc Endovasc Surg*. 2006;32(5):484-90.
  219. Moulik PK, Mtonga R, Gill GV. Amputation and mortality in new-onset diabetic foot ulcers stratified by etiology. *Diabetes Care*. 2003;26(2):491-4.
  220. Brownrigg JR, Davey J, Holt PJ, Davis WA, *et al*. The association of ulceration of the foot with cardiovascular and all-cause mortality in patients with diabetes: a meta-analysis. *Diabetologia*. 2012;55(11):2906-12.
  221. Norlund A, Apelqvist J, Bitzen PO, Nyberg P, *et al*. Cost of illness of adult diabetes mellitus underestimated if comorbidity is not considered. *J Intern Med*. 2001;250(1):57-65.