Part 1

Patient management
Chapter 1

General introduction and outline of the thesis
INTRODUCTION

Today’s medicine, characterized by increased cost, individual patient awareness and medico legal concerns, urges individual health care facilities and medical professionals to obtain and provide detailed insight in quality of provided care. The introduction of numerous diagnostic modalities and therapeutic strategies urges individual physicians and health care facilities to evaluate efficacy and accuracy of the care delivered. This insight in quality of provided care can be used to detect shortcomings in delivered care, evaluate new treatment modalities and initiate new scientific studies. Furthermore monitoring of the provided care increases transparency for physicians, hospitals and patients and can be used to evaluate financial aspects (costs and budget). Also, it provides information to target quality improvement initiatives.

In surgery, it has become more important to evaluate outcomes and to identify indicators of quality of surgical care and there has been a considerable focus on the large number of hospitalized patients experiencing preventable adverse events (AEs). Evaluating AEs can raise the awareness of shortcomings in surgical practice and increase transparency in provided care. Through analysis of AE, one can learn from them, and through study of the cause of the occurrence of the AEs one can try to decrease the number and severity of AEs in the future. Therefore, they can be used as outcome measures to assess the quality of surgical care.

In AE analysis, uniformity of reporting and definition, correction for case mix and for type of surgery performed are essential aspects of evaluating diagnostic and therapeutic care. At first, type of reporting of AEs can be achieved by retrospective medical record review or by routine reporting. However, no gold standard exists for identifying AEs. In cases of comparison of different health care facilities, uniformity of reporting (routine reporting vs. record review) is essential to prevent methodology-related underreporting of AEs. Second, when quality of care among different health care facilities is evaluated by AE registration, a uniform definition of an AE among different health care facilities has to be applied. Third, according to the literature, extensive comorbid conditions are associated with the occurrence of AEs in vascular surgery. Therefore correction for case mix has to be implemented when comparing delivered care among individual facilities. However, exact assessment of pre-operative conditions of patient populations among different health care facilities in order to correct for case-mix is difficult. Not only pre-operative comorbid conditions are strongly associated with adverse outcome, also operations in patients undergoing previous vascular procedures in the unilateral limb are strongly associated with AEs. Therefore, detailed registration of previous vascular interventions in the affected limb should be documented. Furthermore, emergency operations are associated with adverse events compared to elective cases. Therefore also the incidence of emergency interventions has to be taken into account. Fourth, in
vascular BGP surgery, the type of operation performed is strongly correlated with the incidence of AEs. Patients undergoing crural or below knee bypass reconstructions have significant increased chance of unfavourable outcome.

The main focus of this thesis was to evaluate the current status of quality of provided care - and how to improve to quality of care in vascular surgery. We concentrated on the quality improvements in two vascular surgery domains: 1. vascular access surgery because of end-stage renal disease (ESRD) and mainly in 2. lower extremity arterial revascularization (LEAR) because of peripheral arterial occlusive disease (PAOD). However, before addressing these issues, ESRD and PAOD will be described in terms of general definition, diagnosis and treatment. Subsequently patient-based outcomes like functional status and perceived social support (PSS) will be discussed. Finally, the present research will be discussed.

END STAGE RENAL DISEASE (ESRD)

Chronic kidney disease (CKD) is a worldwide public health problem. In the United States, the prevalence of ESRD doubled in the last decade \(^{22,23}\) and is expected to rise further as the U.S. population ages and medical advances result in prolonged survival of individuals with chronic illnesses. The major outcomes of CKD, regardless of cause, include progression to kidney failure, AEs of decreased kidney function, and cardiovascular disease (CVD).

The morbidity and mortality among patients with ESRD is high. Comorbid conditions begin to develop early during the course of CKD. Timely and optimal care during CKD could modify the severity of comorbid conditions and the high mortality among patients with ESRD. Furthermore, improved and timely care during CKD possibly may improve the quality of life of patients with CKD, reduce the incidence of ESRD, and reduce the cost of ESRD care \(^{24-26}\). The care of these patients consumes a significant proportion of health care resources \(^{27,28}\).

Optimal care should involve early diagnosis of renal insufficiency and use of interventions to delay its progression, prevention or attenuation of the expected clinical and biochemical abnormalities of renal dysfunction, modification of comorbid conditions, adequate preparation for ESRD therapy, and timely initiation of dialysis. Therefore, in 1997, the National Kidney Foundation Disease Outcome Quality Initiative (NKF/DOQI) Work Group and European guidelines for vascular access represented a comprehensive consensus statement using evidence-based methods to provide guidelines to optimize care of patients with ESRD \(^{29-31}\).
Diagnosis

According to the NKF/DOQI guidelines, markers for CKD are: persistent proteinuria, abnormalities in urine sediment, abnormalities in blood and urine chemistry measurements and abnormal findings on imaging studies. Persons with a normal glomerular filtration rate (GFR) but with markers of kidney damage are at increased risk for adverse outcomes of CKD. The GFR is the best measure of overall kidney function in health and disease. The normal level of GFR varies according to age, sex, and body size. Normal GFR in young adults is approximately 120 to 130 mL/min per 1.73 m² and declines with age. A GFR level less than 60 mL/min per 1.73 m² represents loss of half or more of the adult level of normal kidney function. Below this level, the prevalence of AEs of CKD increases. In Appendix 1, a summary is listed concerning the stages of ESRD.

History

The history of a possible CKD patient is very important; it reveals a significant amount of information that is needed to eventually perform the best indicated surgical procedure. In case of kidney transplantation the abdominal past history is of great importance for determine the site of the transplantation. The same holds for the placement of the PD catheter, however the site placement of the PD catheter is preferred to be the opposite site of the actual kidney transplantation site in the future. In case of HD, it is important to gain information concerning which extremity is the non-dominant extremity, past history of trauma - and central venous catheters for dialysis, the occupation of the patient and prescribed medication.

Physical examination

In case of kidney transplantation abdominal examination and pulse assessment of femoral artery is important. Concerning HD, preoperative standardised work-up included careful assessment of the vascular anatomy. Arterial examination includes pulse assessment, performance of the Allen test, and bilateral upper extremity blood pressure measurement. Venous examination includes inspection and palpation of the cephalic vein at the wrist and upper arm and the basilica vein at the elbow, with a tourniquet in place.

Duplex ultrasound examination (DUE)

Both arms must be evaluated with DUE by an experienced sonographer. The diameter of the radial artery at the wrist and the brachial artery immediately above the antecubital fossa must be determined. Veins must be assessed on the adequacy of the superficial vein, on ease of compressibility, thickness continuity and depth below the skin. The evaluation of stenosis or occlusion of the deep venous system (axillary and subclavian...
veins) must also be registered. The minimum acceptable threshold for internal diameters for arteries and veins are set at ≥ 2.0 mm according to the guidelines of NKF-DOQI 29-31, the Vascular Access Society 32, 33 and overall HD literature 34, 35.

**Treatment**

Continuous ambulatory peritoneal dialysis (PD) and hemodialysis (HD) are the two principal modalities for maintenance dialysis. However, kidney transplantation is the ultimate successful modality of renal replacement therapy.

**Kidney transplantation**

Kidney transplantation was the first successful modality of renal replacement therapy for irreversible CKD (stage 5); however, its broad applicability has been limited by immunologic rejection, adverse effects of immunosuppressant agents, and a relative shortage of available organs. Notwithstanding strong evidence that transplantation is most successful when implemented before onset of long-term dialysis, only 2.5% of patients with ESRD undergo transplantation as initial renal replacement therapy 36-39. It offers the best survival and QOL for ESRD patients across all demographic groups 39.

**Continuous ambulatory peritoneal dialysis**

PD is well established worldwide as a renal replacement therapy in ESRD patients. It must provide “adequate” replacement of vital renal functions, minimize the potentially harmful effects of the procedure, and take care, to the extent that it can, of the lifestyle and socioeconomic challenges produced by the procedure 40. It is well known that PD is associated with a number of serious AEs. Although improvements in PD delivery systems and connectors have reduced the peritonitis rate to 1 episode every 2 - 3 years 41, peritonitis remains a principal reason to transfer from PD to HD 41, 42. Other recognized causes of PD failure may relate to loss of residual renal function, dialysis adequacy, and patient demands. Furthermore, it is well known that survival of PD patients is significantly improved if they are transferred to HD when PD AEs appear 42, 43.

**Hemodialysis**

Arteriovenous fistulas (AVFs) and arteriovenous grafts (AVGs) are the vascular methods of long-term HD access for patients suffering from ESRD. The Vascular Access Work Group of the NKF-DOQI concluded that the proportion of primary AVFs constructed in all new patients diagnosed with ESRD entering HD should be at least 40% 29-31. The ideal AVFs/AVGs should be durable, pose minimal risk for infection, and require few revisions to maintain ongoing functional patency. However, AVFs and AVGs suffer from a high incidence of primary failure, due to early thrombosis, myointimal hyperplasia or failure
to mature. Vascular access AEs substantially contribute to morbidity and hospitalization in HD patients. Estimates of primary failure, primary- and secondary patency vary considerably. Early thrombosis and failure to mature are significant problems occurring in 20% to 50% of AVFs\textsuperscript{44}. Therefore, prospective identification of patients who are prone to early AVF/AVG failure is of high clinical importance.

**PERIPHERAL ARTERIAL OCCLUSIVE DISEASE (PAOD)**

Atherosclerosis is characterized by narrowing of arteries due to development of plaques, consisting of accumulations of lipids and fibrous elements in the vessel wall. It predominantly affects the circulation of the lower extremity, and therefore causes lower extremity peripheral arterial occlusive disease (PAOD). PAOD is a common syndrome that affects a large proportion of most adult populations worldwide\textsuperscript{45-53}; it affects about 5% of western populations aged between 55 and 74 years\textsuperscript{54,55}. The clinical manifestations of PAOD are a major cause of acute and chronic illness; are associated with decrements in functional capacity and QOL; cause limb amputation and increase risk of death. Patients with PAOD present with a spectrum of clinical manifestations, depending on the degree of ischaemia and the time course of its development. The various risk factors (e.g. smoking, hypertension, cardiac disease, hyperlipidaemia, diabetes mellitus and renal disease) all contribute to the progression of PAOD. Evaluated patients in the following thesis were patients diagnosed with intermittent claudication (IC) or critical lower limb ischaemia (CLI). According to the Society of Vascular Surgery/North American Chapter of the International Society for Cardiovascular surgery (SVS/ISCVS)\textsuperscript{56,57}, the Rutherford clinical categories and Fontaine clinical classification (Appendix 2) used to classify the degree of claudication, ischemia and salvageability of the limb.

**Diagnosis**

Concerning the diagnosis of PAOD of the lower extremities, there are three important cornerstones: anamnesis, physical examination and imaging.

**History**

The history of a possible PAOD patient is very important; it reveals a significant amount of information that is needed to eventually draw the exact diagnosis. There is a high susceptibility of IC when the complaints are defined as extremity pain, discomfort, or weakness that is consistently produced by the same amount of walking or equivalent muscular activity in a given patient and that is promptly relieved by cessation of that activity (rest < 10 minutes) with a pain free walking distance (PFWD) of > 100 meters.
(Fontaine 2a) and a PFWD of < 100 meters (Fontaine 2b) 45, 49, 50, 52, 56, 57. However, there is a high susceptibility of CLI if the complaints (defined as the presence of the following symptoms for > 2 weeks) were defined as ischaemic rest pain (Fontaine 3) and gangrene or nonhealing ischaemic ulceration (Fontaine 4) 45, 49, 50, 52, 56, 57.

Physical examination

A clinical examination that is specifically targeted to the diagnosis of PAOD yields a low rate of detection and is blurred by observer error. Nevertheless, comprehensive physical examination still remains an integral part of the evaluation of patients at risk for PAOD. The physical examination should assess the circulatory system as a whole. Key components of the general examination include measurement of blood pressure in both arms. The specific peripheral vascular examination requires palpation of the femoral, popliteal, dorsalis pedis and posterior tibial artery pulses. They should be assessed in both legs. Also important is the assessment of the presence of ischemic ulcers or gangrene. Less specific aspects of the physical examination for PAOD include changes in color and temperature of the skin of the feet, muscle atrophy from inability to exercise, decreased hair growth and hypertrophied, slow-growing nails 45, 49, 50, 52, 56, 57.

Ankle-brachial index (ABI)

The ABI to date has proved to be the most effective, accurate, and practical noninvasive vascular laboratory test in PAOD detection. It can be performed by the primary care provider in the office, or at bedside in hospitalized patients 45, 49, 50, 52, 56, 57. Measuring the pressure in the ankle arteries has become a standard part of the initial evaluation of patients with suspected PAOD. The ABI provides considerable information. A reduced ABI in symptomatic patients confirms the existence of hemodynamically significant occlusive disease between the heart and the ankle; with a lower ABI indicating a greater hemodynamic severity of occlusive disease. The typical cut-off point for diagnosing IC is ≤ 0.90 at rest 45, 49, 50, 52, 56, 57 : with a PFWD > 100 meters (Fontaine classification 2a) and an ankle pressure (AP) after exercise > 50 mmHG, or a PFWD < 100 meters and an AP after exercise < 50 mmHG (Fontaine classification 2b). This corresponds with categories 2 and 3 of the SVS/ISCVS reporting standards 56, 57. However, the diagnosis of CLI should be confirmed by the ABI, ankle pressure (AP) or toe systolic pressure (TP). Ischemic rest pain most commonly occurs below an AP of <50-70 mmHg or TP of <30-50 mmHg 36, 40, 41, 43. This corresponds with categories 4, 5 and 6 of the SVS/ISCVS reporting standards 56, 57.

Doppler

Examination with a pen probe, including measurement of the ABI, or of segmental arterial pressure, is used in screening for hemodynamically significant stenoses of the
aortoiliac and femoropopliteal arteries; however, it cannot accurately quantify either severity of extent of PAOD.

**Imaging**

**Duplex ultrasound examination (DUE)**
The DUE of the lower-extremity vasculature may be useful to screen patients with PAOD, to assess candidacy for either surgical or endovascular revascularization. Disadvantages include the length of the examinations, variability of skill of the technologist and crural arteries are challenging to image in their entirety. Arterial flow velocity can be assessed using a continuous wave at multiple sites in the peripheral circulation. When assessed over the posterior tibial artery, a reduced or absent forward flow velocity was highly accurate for detecting PAOD. However, it is operator-dependent.

**Computed tomographic angiography (CTA)**
Potential side effects and contraindications should be considered in choosing the imaging modality. Invasive CTA requires contrast medium that is potentially nephrotoxic. However, CTA is of major value in localizing an obstruction and visualizing the distal arterial tree. It also assists in distinguishing the kind of LEAR: endovascular or surgical procedures. CTA may also be used in the setting of PAOD to diagnose and delineate the extent of disease. The advantages of CTA include its speed, convenience and ability for cross-sectional imaging of the vessel.

**Digital subtraction angiography (DSA)**
This catheter-guided invasive technique enables therapeutic intervention in terms of PTA, which is a well-accepted therapy in the treatment of stenosis and occlusion in patients with PAOD. DSA involves a recording technique whereby the fluoroscopic image is amplified and digitized, allowing for subsequent processing by many means that can enhance visualization of the structures of interest. Also important to mention are image contrast, brightness, edge enhancement, sharpness, and even the colour of the contrast agent can be modified before storing the image.

**Magnetic resonance angiography (MRA)**
MRA has been developed to provide a noninvasive alternative; it is an accurate method used to depict significant stenoses and occlusions in lower extremity arteries. The major advantages of MRA are the absence of X-ray exposure for the patient and investigator, lack of nephrotoxic iodinated contrast media administration and reduction of allergic reactions, three-dimensional vascular delineation of the arterial tree and excellent bone and soft-tissue contrast.
Classification of lesions

The Trans Atlantic Inter-Societal Consensus (TASC I-II) guidelines contain a classification system for treatment of PAOD. The classification is based upon response to intervention and is independent of technology and techniques. The goal of this system is to indicate the best form of LEAR, endovascular (TASC A) or surgical (TASC D), for patients with lower-extremity PAOD. Those lesions without strongly supportive evidence, but with a greater likelihood of good response to endovascular (TASC B) or surgery (TASC C), are noted as critical issues requiring additional assessment.

INTERMITTENT CLAUDICATION (IC)

The annual incidence of IC is more difficult to measure and probably less important than its prevalence (unlike the case of the relatively very much smaller number of patients with CLI). The prevalence of IC would appear to increase from about 3% in patients aged 40 to 6% in patients aged 60 years. It is difficult to predict the risk of deterioration in a recent claudicant. Though highly prevalent, the natural history of IC is relatively benign with deterioration to CLI occurring in 25% to 30% over five years and amputation in only 1% to 2%. Despite the rather benign prognosis for the limb, IC is an ominous sign of systemic atherosclerosis with considerable overlap of disease manifested in multiple vascular beds, coupled with an increased cardiovascular morbidity. The major risk facing patients with IC is mortality from cardiovascular causes, 30% at 5 years. Patients with IC have sufficient blood flow so that limb ischemic symptoms are absent at rest. With increased local muscular demand for metabolic support during exercise, blood flow in individuals with lower extremity PAOD is inadequate to meet this demand, and limb muscular fatigue and/or pain results. In this study IC was defined as extremity pain, discomfort, or weakness that is consistently produced by the same amount of walking or equivalent muscular activity in a given patient and that is promptly relieved by cessation of that activity. The symptoms are most commonly localized to the calf, but may also affect the thigh or buttocks.

CRITICAL LIMB ISCHAEMIA (CLI)

There will be approximately between 500 and 1000 new cases of CLI every year in a European or North American population of 1 million, and the prevalence has been estimated to be 1 per 2500 inhabitants. Patients with CLI represent about 1% of the total number of patients with PAOD. PAOD patients have a 3 to 5 times overall greater risk of cardiovascular mortality than those without this disease. However CLI
patients have an even greater risk of experiencing cardiovascular ischemic events. After major LEAR, CLI patients have a 30-day mortality between 5-7% Mortality is expected to be around 20% within the first year of presentation, 40-75% of the CLI patients are likely to die within 5 years, mainly as a result of cardiac AEs. The 10-year survival rate in CLI is as low as 25%. Over 25% of CLI patients will require major amputation. Patients with CLI have resting perfusion that is inadequate to sustain viability in the distal tissue bed. Ischemic rest pain most typically occurs at night but in severe cases can be continuous. The pain is localized in the distal part of the foot or in the vicinity of an ischemic ulcer or gangrenous toe. The pain often wakes the patients at night and forces them to take a short walk around the room. Often, patients sleep with their ischemic leg dangling over the side of the bed. In severe cases, sleep becomes impossible because pain sets in after only a short period of supine rest, causing in many patients a progressive further decline of their general physical and psychological condition. Patients with CLI may also present with ischemic ulcers or gangrene.

**Treatment**

The management of PAOD patients is aimed at risk factor modification, relief of symptoms and improvements of quality of life (QOL). The primary goal of IC treatment is to relieve reversible muscle ischemia during walking that is characterized by cramping and aching in the affected muscle. However, the primary goals of the CLI treatment are to relieve ischemic pain, heal ischemic ulcers, prevent limb loss, improve patient function and QOL and prolong patient survival. The treatment options can broadly be classified into non-invasive, endovascular and surgical (vascular and non-vascular) treatment.

**Non-invasive treatment**

It indicates all treatment strategies outside the operating room. It often consists of lifestyle modification (LSM) and secondary prevention (SP). LSM, such as smoking cessation, dietary management, and exercise, is very important when treating risk factors in PAOD. It has been proven that regular supervised exercise increases the pain-free and maximum walking distance in patients with IC. Important to stress is that supervised exercise therapy has statistically significant benefits on treadmill walking distance compared with non-supervised regimens, which is currently the main prescribed exercise therapy for people with intermittent claudication. SP, such as lipid-lowering agents (LLA), antiplatelet agents (APA), heart rate lowering agents (HRLA) and blood pressure lowering agents (BPLA) has been shown to be effective in decreasing the risk of cardiovascular morbidity and improving long-term survival. Also included are strategies like local pain or wound management and/or antibiotic therapy. Pain management is essential in improving function and QOL.
The hallmark of CLI is ischemic rest pain and painful ulceration. Pain control is a critical aspect of the management of these patients. Wound infection should be identified as early as possible and its level of involvement assessed and aggressively treated.

**Endovascular treatment**

The aim of invasive treatment of PAOD is to improve functioning by improving blood flow. Invasive treatment is generally considered for patients with severe functional limitation, such as life-style limiting IC, or potential for limb loss. It consists of percutaneous transluminal angioplasties (PTAs) and/or stent placement and percutaneous intentional extraluminal (subintimal) revascularization (PIER).

**Percutaneous transluminal angioplasty (PTA)**

The aim of the PTA is to achieve in-line repair of the artery. Therefore four important characteristics of the lesion significantly influence the difficulty of the procedure and its expected outcome. At first the location of the lesion: proximal, larger caliber arteries offer the best initial and long-term results, with progressively decreasing long-term patency rates for more distal dilatation sites. PTAs of the common iliac artery have better patency rates compared to PTAs of the femoropopliteal artery (60% vs. 38% at 5 years). Second, is the lesion a stenosis or an occlusion: the initial and long-term results of endovascular reconstruction are better for stenoses than for occlusions. Technical failure occurs in 10% to 20% of iliac occlusions but only 1% to 5% of iliac stenoses. Third, the length of the lesion: the longer the stenosis, the lower the patency rate after PTA. At last, the presence of multiple stenoses: lesions composed of multiple stenoses present more potential sites for dissection, residual stenosis, or recurrent stenosis.

**Percutaneous intentional extraluminal (subintimal) revascularization (PIER)**

The technique of PIER is dependent on the presence of normal vessel above and below the occlusion to allow access. It can play an important role in the treatment of PAOD, especially in the case of CLI. After 1 year, the clinical success is between 50% and 70%, primary patency was around 50% and limb salvage varied from 80% to 90%. Despite the moderate patency rates after one year, PIER may serve as a “temporary bypass” to provide wound healing and LS.

**Surgical treatment**

It consists of revascularization and amputation and/or necrotectomy.

**Revascularization**

Endarterectomy is a reliable method for restoring patency of the artery. It is carried out by separating the atheromatous plaque from the arterial wall. The aim of a BGP is
‘replacement’ of the artery. Autogenous veins should be used whenever possible for infrainguinal BGP. It has a better long-term patency than prosthetic in the infrainguinal region\textsuperscript{112}. Over the short term, polytetrafluoroethylene (PTFE) has delivered near equivalent results in the above-knee position. However the use of PTFE to the infrapopliteal arteries suggests much less satisfactory long term results; their patency is significantly lower once the knee joint is crossed (5-year patency: primary 30.5% secondary 39.7%)\textsuperscript{113-118}. Therefore assessment of the availability and quality of autogenous veins with DUE mapping is important preoperatively. The greater saphenous vein, either in a reversed or in situ configuration offers the best match of size and quality. In its absence, other venous tissue including contralateral long saphenous vein, short (lesser) saphenous vein, femoral vein, arm vein, PTFE or Dacron can be used.

Amputation and/or necrotectomy

The non-vascular surgical treatment consists of drainage/debridement, minor amputations, defined as toe (TA) - or transmetatarsal amputation (TMA), and a major amputations, defined as an amputation below (BKA) -, through (TKA) - or above (AKA) the level of the knee.

Risk factors and comorbidity

The management of the patient with PAOD has to be planned in the context of the epidemiology of the disease, its natural history and, in particular, the modifiable RFs for the systemic disease as well as those that predict deterioration of the circulation to the limb. As mentioned, the major cause of PAOD is atherosclerosis. RFs for atherosclerosis such as cigarette smoking, diabetes mellitus, hyperlipidaemia and hypertension increase the likelihood of developing PAOD, as they do for other manifestations of atherosclerosis\textsuperscript{45, 49, 50, 52, 53, 56, 57}.

Standardized registration

In order to obtain insight in RF incidence and prevalence, a well documented and validated registration of RFs on PAOD is paramount. Smoking, hypertension, cardiac disease, hyperlipidaemia, diabetes mellitus, renal disease, pulmonary disease carotid disease, age and patients risk score can be classified according to the SVS/ISCVS\textsuperscript{56, 57}, TASC I\textsuperscript{45} and TASC II\textsuperscript{40} and the American Heart Association/American College of Cardiology (AHA/ACC) guidelines\textsuperscript{41, 43, 44, 47}. The American Society of Anaesthesiologists (ASA) classification\textsuperscript{119, 120} and body mass index (BMI)\textsuperscript{121} of patients must be determined according to their general condition. Lipid abnormalities can be classified according to the National Cholesterol Education Program (NCEP)\textsuperscript{122, 123}.

Blood pressure regulation (BPR) can be classified according to the Joint National Committee on prevention, detection,
evaluation, and treatment of high blood pressure (JNC VI) \(^{124}\), the New York Heart Association (NYHA) guidelines \(^{50}\) and the guidelines of the World Health Organization and International Society of Hypertension (WHO/ISH) \(^{125}\). Also diabetes mellitus (DM) can be defined according to the intercollegiate Guidelines Network (SIGN) \(^{126}\).

**Secondary prevention**

The aim of treatment in patients with PAOD is to relieve lower extremity symptoms by interventions such as regular supervised exercise, endovascular therapy, or surgery and to reduce the risk of generalized atherosclerosis by treatment of RFs. RF modification to minimize the risk of vascular morbidity and mortality requires major changes in lifestyle, behavior and drug therapy, such as smoking cessation and pharmacologic treatment. The pharmacologic treatment of the cardiovascular comorbidities in PAOD patients can have a profound effect on the outcomes of these patients; they can generally be grouped into 5 categories: lipid-lowering agents (LLA), antiplatelet agents (APA), heart rate lowering agents (HRLA), blood pressure lowering agents (BPLA) and glucose lowering agents (GLA).

**Anti platelet agents**

The use of APA is indicated as secondary cardiovascular prevention in patients presenting with PAOD. All symptomatic PAOD patients with or without a history of other cardiovascular disease should be prescribed APA long term to reduce the risk of cardiovascular AEs and mortality. Patients who withdraw APA prior to the event have worse outcomes than those who either continued on APA or those who have never received APA \(^{51, 88, 90, 91, 127-131}\).

**Heart rate lowering agents**

According to the DECREASE-I trial \(^{132}\), and outlined in latest AHA/ACC guidelines on perioperative management of patients with PAOD \(^{133}\) initiate β-blocker treatment (bisoprolol 2.5 mg, initiated at least 30-day prior to surgery) in patients with 1 or more cardiovascular clinical risk factors to achieve perioperative heart rate between 65-70 \(^{48, 87, 128, 131, 132, 134-146}\).

**Blood pressure lowering agents**

According to the HOPE-trial \(^{86}\) and the ABCD-trial \(^{147}\), there is a beneficial effect of ACE-inhibitors (ACEi) (ramipril, enalapril) in PAOD patients. In the latest AHA/ACC guidelines on perioperative management of patients with PAOD \(^{133}\), ACEi may be considered for cardiovascular risk reduction.
Lipid-lowering agents

LLA, especially using statins, has been shown to dramatically improve outcome of subjects with proven atherosclerotic cardiovascular disease (HPS-trial) 88. Accordingly, most if not all guidelines recommend treatment with statins in all SP patients including PAOD patients. Favourable influences on leg functioning, walking performance and positive effects on the arterial wall structure and function has been described 88, 146, 148-159. The major proven consideration to prescribe LLA to PAOD patients is the prevention of cardiovascular death (mortality) and (recurrent) major cardiovascular events (morbidity) such a myocardial infarction 88, 128, 146, 148, 149, 160-162.

Glucose lowering agents

Patients with diabetes mellitus and PAOD should have aggressive control of blood glucose levels with a haemoglobin A1c (HgbA1c) goal of <7.0% or as close to 6% as possible. Aggressive diabetes mellitus control decreases microangiopathy and its related AEs and may decrease vascular mortality and morbidity rates 163.

Adverse events

In order to evaluate provided care analysis of process, structure and outcome indicators are frequently described in literature 164, 165. One of the most studied outcome indicator is assessment of incidences of AEs. Due to extensive comorbid conditions and technically challenging surgical revascularization procedures, patients treated for PAOD are at high risk for developing AEs. Rutherford et al 56, 57 proposed an AE registration classification. However, literature shows inconsistency in defining, documenting and classifying AEs resulting in diverse interpretations of AE analysis 10, 166-170. The Association of Surgeons of the Netherlands (ASN) 8, 16, 171 has developed a uniform definition of an AE. Three teaching health care facilities in the Netherlands: the Department of Vascular Surgery of the Leiden University Medical Centre (LUMC) 16, 171-174, the Department of Vascular Surgery of the St. Elisabeth Hospital in Tilburg (EH) 8, 10, 175 and the Department of Vascular Surgery, HagaHospital, location Red Cross and location Leyweg in the Hague (RCH) 3, 6, 9, 11, 17, 117, 176-183 have been documenting AEs prospectively according to this definition for more than 15 years.

Definition

The ASN developed a general definition of an AE. This definition differs from that used in other studies because it has been chosen with the explicit aim of excluding subjective judgment on cause and effect, and right and wrong. The definition of an AE is: “an unintended and unwanted event or state occurring during or following medical care, that is so harmful to a patient’s health that (adjustment of) treatment is required or that
permanent damage results. The AE may be noted during hospitalization, until 30 days after discharge or transferee to another department. The intended result of treatment, the likelihood of the adverse outcome occurring, and the presence or absence of a medical error causing it, is irrelevant in identifying an adverse outcome”. All three health care facilities registered an AE according to this definition. This definition did not change during the study period.

**Leiden University Medical Centre (Leiden)**

There is a long tradition of AE reporting in the surgical department of the Leiden University Medical Centre, going back to the beginning of the 1980s. The presence and completeness of each patient’s form is checked weekly. Written information on AEs is checked and discussed 2 weeks after discharge at a weekly meeting attended by all surgeons, residents, interns, and medical students. Reported AEs are entered into dedicated software and are automatically encoded on a three-dimensional encoding system according to (1) nature, (2) location and (3) determinants and other relevant information. Furthermore, for each adverse outcome the severity of its impact on the patient’s health is registered in four categories.

**St. Elisabeth Hospital (Tilburg)**

In 1993 a fully automated registration system was implemented in the surgical department of the St. Elisabeth Hospital in Tilburg, the Netherlands. In 1995 a total coverage was reached, and registration of AEs was also possible in the intensive care unit, operating room, emergency department, and outpatient clinic as well. Since 1995 a system was used based on an elaborated list of criteria developed by the ASN as listed in Appendix 4 and 6. A complication is identified by one of the physicians in the surgical team who documents the complication in an electronic medical file real time. This file is operational throughout the hospital and the outpatient clinic, which makes recording easy. In-hospital and at the outpatient clinic documented complications are automatically presented at the daily surgical conference and discussed.

**Haga hospital (The Hague)**

In 1993 a fully automated registration system was implemented in the surgical department of the surgical department of the Red Cross Hospital in The Hague, the Netherlands. In 1995 AEs were registered in a standardized way. All AEs that occur in patients admitted to the surgical department are documented twice a day during a briefing in the morning and the afternoon. AEs were coded according to our AE registration system on a weekly basis. All senior surgeons, all surgical residents, and interns joined this weekly meeting. All AEs that occurred during a patient’s hospital stay are included in this database. The registration of AEs is divided into two categories as listed in Appendix
5 and 6. The first category describes the cause for the occurrence of the AE. The second category describes the consequence of an AE. An AE was coded once in both categories. Classification was stringent.

**Quality of life (QOL)**

In cardiovascular research, formal patient based outcome measures such as QOL are becoming increasingly important \(^{184-186}\). Hence, inclusion of patient-based outcomes is particularly relevant in the evaluation of the quality of care for these patients \(^{187-191}\). However, the interpretation and comparison of the available studies on QOL in patients with PAOD is difficult due to various definitions used for QOL. According to the World Health Organization (WHO) \(^{192,193}\), QOL assesses the patient’s own perception of his/her physical, social and emotional functioning. It reflects the relative weight patients give to their different dimensions and it indicates the way patients feel about their functioning \(^{190}\).

**Perceived social support (PSS)**

In contrast with QOL studies, research focusing on the PSS on PAOD is scarce. It is a validated tool to objectify this attribute \(^{194}\). Three sources of PSS are addressed, i.e., family, friends, or significant other. The scale and its subscales are inversely related to both depression and anxiety. The PSS is validated across a number of healthy and somatic populations \(^{195,196}\).

**Functional status**

Functional status is an important postoperative outcome indicator after LEAR for patients with CLI. The functional status evaluated according to the functional independence measure \(^{197}\).

**RATIONALE AND AIMS OF THIS THESIS**

This thesis describes several follow-up studies in patients diagnosed with ESRD or PAOD (IC and CLI). Between the period of January 1999 and January 2008, consecutive patients presenting at the vascular outpatient clinic of the three health care facilities, LUMC, SEH and the RCH, were included. The studies described in the present thesis are based on these data.
Part 1: patient management

The first part of the thesis consisted of (1) a systematic review of quality initiatives in vascular surgery, (2) a systematic review to assess the implementation of established secondary preventive (SP) measures in patients with PAOD and (3) the assessment of the implementation of a new optimised care protocol (OCP) outlined in a multidisciplinary meeting in vascular access surgery in ESRD patients.

**CHAPTER 2** is a systematic review concerning all quality initiatives in vascular surgery. In this chapter, insight in strategies to optimize quality of care by process, structure and outcome parameter evaluation is provided. The aim of **CHAPTER 3** was to perform a systematic review to assess the implementation of established recommended SP measures in PAOD patients with IC or CLI using past ten years (from 1999 till June 2008) literature concerning SP in PAOD patients. Assessment of study quality was done following the Cochrane Centre review system. The record outcomes were anti-platelet agents (APA), heart rate regulation (HRR), blood pressure regulation (BPR), lipid-lowering agents (LLA), glucose lowering agents (GLA), smoking cessation and walking exercise. **CHAPTER 4** aims to evaluate the effectiveness of a predetermined OCP monitored in a bimonthly multidisciplinary meeting for vascular access surgery of AVFs and AVGs for haemodialysis which was introduced in January 2004. Therefore, the objective of this chapter was (1) to evaluate the incidence of surgical and endovascular revisions and (2) to compare the primary and secondary patency rates between the historical control group and the group treated using the OCP.

Part 2: adverse events

The second part of this thesis evaluates (1) possible risk factors for AE occurrence by assessing three different health care facilities, (2) cardiac AE after primary LEAR for CLI in order to evaluate the impact of cardiac AEs on the clinical outcome and (3) the average estimated total costs after treatment for PAOD.

**CHAPTER 5** focuses on determining risk factors for AE occurrence by assessing three different health care facilities. The goal of this chapter was to assess independent risk factors for AE occurrence after peripheral arterial bypass graft surgery: patient, disease and operation characteristics besides general differences between health care facilities. Secondary goal is to provide an overview of potential advantages and limitations of AE registration as an indicator of quality of care of individual health care facilities in general and among different health care facilities in particular. The objective in **CHAPTER 6** was (1) to assess the occurrence of adverse events (AE) after LEAR for CLI, and (2) to examine the impact of AEs on the clinical outcome of the CLI patients’ general health. This cohort was divided into patients with - and without AEs. AEs were categorized according to
Predefined standards: minor, surgical, failed revascularization and systemic. The consequences of AEs were reoperation, additional medication, irreversible physical damage and early death. An appraisal of economic outcome of AEs is assessed in **CHAPTER 7**.

The goal of this chapter was to perform a detailed cost evaluation which was performed of patients admitted and treated for PAOD. In this chapter, the actual costs of primary treatment including pre-operative work-up and primary intervention were assessed. Furthermore, secondary AE related costs were identified. Also, cause and consequence of AEs were registered and related expenses assessed.

**Part 3: quality of life**

The third part of this thesis focuses on the QOL of the PAOD after primary LEAR, divided in (1) role of social support in PAOD on the outcome and (2) the improvement of functional status of PAOD patients after primary LEAR.

**CHAPTER 8** focuses on short-term outcomes after LEAR in patients with IC and aims to evaluate the role of PSS on in-hospital length of stay (LOS) and examine whether differences with regard to type of revascularization procedure are related to the level of PSS. Assessment of perceived social support (PSS) by PSS-scale, divided in: low PSS vs. high PSS. Primary endpoints were relationship between PSS and in-hospital length of stay (LOS) and differences in lower extremity arterial revascularization (LEAR) based upon PSS. Subsequently, **CHAPTER 9** describes an assessment of what factors may be of importance in determining functional status after primary LEAR for CLI. It also determined the outcome of functional status by evaluating ambulatory status undergoing primary LEAR for CLI. This cohort was divided into ambulatory (group I) - and nonambulatory (group II) patients before LEAR (between January 2001 - January 2003) and during follow-up (3 years and 6 years).

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