The long-term prognosis of patients with peripheral arterial disease after infrainguinal bypass surgery

The follow-up of the Dutch Bypass and Oral anticoagulants or Aspirin Study

Eline S. van Hattum

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Voor mijn ouders, Annemarie en Daan

Contents

Chapter I

General introduction and
outline of the thesis

Peripheral arterial disease

Epidemiology and pathophysiology

Peripheral arterial disease (PAD) is characterised by a progressive narrowing or occlusion of the major arteries in the lower limbs as a result of atherosclerosis. PAD has a high incidence and prevalence, but often goes unnoticed as approximately two thirds of patients with PAD are asymptomatic.[1,2] The prevalence of symptomatic PAD ranged between 3% and 11%.[1-4] However, the overall prevalence, including asymptomatic PAD, was reported up to 30% at ³70 years of age.[4] The prevalence of PAD strongly increases with age. Persons in their forties have a prevalence of about 1%, which increases to 5% in their sixties, and reaches 15% to 20% at an age over 70 years.[3,5] Other factors associated with PAD are male sex[6,7], black race[8], smoking[9], diabetes[10], hypertension[11], renal insufficiency[12,13], dyslipidaemia[14], C-reactive protein[14], and fibrinogen[14].

Diagnosis and clinical manifestations of PAD

An important diagnostic tool for PAD, besides a detailed medical history, risk factor assessment, and physical examination of arterial pulses and atherosclerotic signs, is the ankle-brachial index (ABI). The ABI is an easy, quick, inexpensive, and non-invasive measurement to determine PAD, especially when PAD is asymptomatic. PAD is defined by an ABI of 0.9 or less, which is calculated by dividing the systolic blood pressure in the tibial or pedal arteries by the pressure in the brachial artery in rest.[15] The ABI has a considerable sensitivity and specificity, ranging between 61% to 91% and between 82% to 90%, respectively.[16-18]

In that one third of patients in whom PAD does become symptomatic, the most likely first clinical presentation is intermittent claudication.[19,20] Intermittent claudication is defined by a cramping discomfort in the calf provoked by walking and relieved in rest within several minutes.[19] This cramping discomfort results from an imbalance between the increased oxygen demand of the muscles during exercise and the limited oxygen supply through the stenotic arteries. In rest this imbalance is corrected and the complaints dissolve. However, if atherosclerosis progresses, this imbalance can also occur in rest and the cramping pain in the lower limb may become chronic. Ischaemic lower limb pain that is present for more than two weeks with or without tissue loss (i.e. ulcers or gangrene) is defined as critical limb ischaemia.[20]

Besides lower limb complications, patients with PAD are at high risk of cardiovascular and cerebrovascular ischaemic events, because PAD is part of a systemic disease.[21,22] Atherosclerosis affects the whole arterial system with the term PAD merely summarizing its manifestations in the legs, as the term coronary artery disease (CAD) does for atherosclerotic manifestations in the heart, and cerebrovascular disease (CVD) in the brain. In 2% to 6% of PAD patients atherosclerosis is symptomatic in a second

arterial bed at the same time and in a third arterial bed in 1% to 2%. In comparison with patients with CAD or CVD, patients with PAD have the highest risk of all-cause or vascular death, and the second highest risk of myocardial infarction and stroke.[22] Despite the growing awareness that asymptomatic PAD is an important marker of generalized atherosclerosis, the systemic consequences even of symptomatic PAD are still underestimated in comparison with the presence of CAD or CVD.[23]

Treatment of PAD

Non-interventional treatment

Rapid progression of atherosclerotic disease is prevented by management of cardiovascular risk factors and co-morbidities through lifestyle modification and drug therapy. Important lifestyle modifications are regular exercise for at least 30 minutes 5 to7 times a week, a diet that is low in saturated fat, weight reduction, and cessation of smoking.[24] The preferred body mass index (BMI) is below 25. An alternative measurement for body fat is the waist circumference. A waist circumference above 102 cm in men and above 88 cm in women indicates an excess of intra-abdominal visceral fat, which is a strong predictor of an adverse cardiovascular outcome.[25] Abdominal obesity together with insulin resistance, aging, and physical inactivity are thought to give rise to the risk factors that comprise the metabolic syndrome.[26] The risk factors of the metabolic syndrome are hypertension, an elevated plasma glucose level, and dyslipidaemia.[26] Dyslipidaemia consists of an elevated low density lipoprotein (LDL) level (>2.6 mmol/L), an elevated triglyceride level (>1.7 mmol/L), and a reduced high density lipoprotein (HDL) level (in men, <1.0 mmol/L; in women, <1.3 mmol/L).[24] Patients with the metabolic syndrome are at an increased risk of CAD, CVD, PAD, and diabetes type II.[26] In treating the metabolic syndrome, lifestyle modifications should be introduced first before starting drug therapy.[26 7]

Drug therapies for atherosclerotic risk factors

Guidelines recommend to control the blood pressure in hypertensive PAD patients below a systolic pressure of 140 mmHg and a diastolic pressure of 90 mmHg for prevention of ischaemic events.[27] In diabetics the systolic pressure should be less than 130 mmHg and the diastolic pressure less than 80 mmHg.[27] Any agent able to lower blood pressure is suitable for prevention of ischaemic events in PAD patients.[27] Some guidelines recommend angiotensin converting enzyme (ACE) inhibitors as drug of first choice.[24] This is because the ACE-inhibitor ramipril has shown to reduce mortality in PAD patients with a relative risk reduction of about 25% in comparison with placebo.[28] Beta-blockers showed a similar risk reduction of mortality in patients after myocardial infarction[29], but also demonstrated to be less protective of strokes in patients with CVD.[30] Therefore, the choice of antihypertensive drug should be based on a patient's medical history and current drug treatments.[27] Other suitable blood pressure lowering agents in patients with PAD are thiazide diuretics, angiotensin-II receptor antagonists, and calcium channel blockers.[31]

When treating dyslipidaemia it is recommended to aim for the target level of each lipid fraction separately instead of treating the total cholesterol level (<5.2 mmol/L).[32] All patients with PAD, either symptomatic or asymptomatic, should have an LDL level of less than 2.6 mmol/L.[24,32] In case PAD patients have an additional vascular disease in another arterial bed (i.e. CAD or CVD) the LDL level should be less than 1.8 mmol/L.[24,32] Statins are recommended as the drug of first choice.[24,32] Fibrates and nicotine acid are more effective in lowering triglyceride levels and raising HDL levels than lowering LDL levels and should therefore be added to statin therapy when multiple abnormalities in the lipid spectrum are present.[32]
In patients with diabetes the plasma glucose level should be controlled below 7% glycaeted haemoglobin (HbA_{1c}) or as close to 6% as possible through lifestyle modification and drug therapy.[24] The drug of first choice in the medical management of diabetes type II is metformin which mainly suppresses the hepatic glucose production.[33] Other effects of metformin are an increase in insulin sensitivity, peripheral glucose uptake, fatty acid oxidation, and a decrease in absorption of glucose from the gastrointestinal tract.[33] When the glycaemic control is insufficient a second drug should be added to metformin, which is either insulin or a sulfonylurea.[33] If the glycaemic control remains insufficient insulin therapy should be intensified. Other antihyperglycemic agents are glinides, alfa-glucosidase inhibitors, glucagon-like peptide-1 agonists, amylin agonists, and dipeptidyl peptidase four inhibitors.[33]

Antithrombotic therapies
Antithrombotic therapy is highly effective in reducing the risk of ischaemic events in patients with atherosclerotic disease. Two major types of antithrombotic drugs are distinguished: oral anticoagulants and antiplatelets. Oral anticoagulants inhibit the function of vitamin K which is required for activation of several coagulation factors.[34] Antiplatelet drugs inhibit platelet adhesion, platelet aggregation, or both.[35] Both types of antithrombotics have been shown to be equally effective in preventing ischaemic events.[36,37] Oral anticoagulants have been shown to reduce the risk of lower limb amputation with at least 50% and all-cause death with at least 30% at two and five years after peripheral bypass surgery in patients with PAD.[38] Antiplatelet drugs, such as aspirin, have been shown to reduce the risk of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death with a relative risk reduction of about 23% in patients with PAD.[39,40] In the Dutch Bypass and Oral anticoagulants or Aspirin (BOA) Study no statistical significant differences were seen in the prevention of all-cause death, vascular death, myocardial infarction, and lower limb amputation between patients treated with aspirin or oral anticoagulants.[37] However, the Dutch BOA Study did find a non-significant trend favouring oral anticoagulants for the prevention of the composite outcome event of vascular death, non-fatal myocardial infarction, non-fatal ischaemic stroke, and lower limb amputation (hazard ratio [HR], 0.89; 95% confidence interval [CI], 0.75 to 1.06), but the trial was underpowered to demonstrate

a statistically significant difference.[37] A reduced risk of ischaemic stroke was found in the oral anticoagulant group (HR, 0.50; 95% CI, 0.28 to 0.89) and a twofold higher risk of bleeding, including haemorrhagic strokes (HR, 1.96; 95% CI, 1.42 to 2.71).[37] Although antiplatelets also increase the risk of extracranial bleeding substantially, oral anticoagulants increase the risk even more. The greater risk of bleeding together with the need for monitoring of the international normalized ratio (INR) and frequent dose adjustments have made the treatment with oral anticoagulants less favourable than with antiplatelets. Therefore, lifelong use of aspirin is advised at a minimum dose of 75 mg a day and a maximum dose of 100 mg a day in patients with PAD.[24,41] Patients who do not tolerate aspirin are recommended clopidogrel 75 mg a day as an alternative[24,41], based on one randomised trial that showed a 24% relative risk reduction of cardiovascular events in PAD patients treated with clopidogrel versus aspirin with similar bleeding risks in both treatment groups.[42]

The combined treatment of oral anticoagulants plus aspirin cannot be recommended in PAD patients, because the combined treatment did not prevent more ischaemic events than aspirin alone, but did induce more bleeding events.[36] The same was seen for the dual antiplatelet therapy of aspirin plus clopidogrel versus aspirin alone.[43] Although slightly more myocardial infarctions were prevented in the dual antiplatelet group (3.7% vs. 2.3%; HR, 0.63; 95% CI, 0.42 to 0.96), more minor bleedings had occurred (odds ratio, 1.99; 95% CI, 1.69 to 2.34).[43]

Interventional treatment

Although PAD progresses pathologically, its symptoms remain fairly stable over time.[44,45] Only about 25% of PAD patients require local treatment.[44,45] Local treatment of disabling intermittent claudication or critical limb ischaemia consists of revascularisation by means of endovascular or open vascular repair.[24] Open vascular surgery with endarterectomy or bypass surgery is the oldest approach. Bypass surgery originated in the 19th century. In 1897 James B. Murphy was the first to report that an arterial anastomosis was applied in humans.[46] Alexis Carrel continued to refine Murphy's procedure by connecting the ends of two blood vessels in line instead of inserting one end of the blood vessel into the other.[47] He won the Nobel Prize in 1912. At the same time, José Goyanes Capdevila experimented with veins for the repair of arteries.[48,49] In 1948 the French surgeon Jean Kunlin was the first to describe a peripheral bypass procedure of an occluded artery with the patient's own saphenous vein.[50] However, until the 1960s surgeons were reluctant to perform venous bypass surgery because of the reported aneurismal complications of the anastomosis. Gradually, the growing number of successes achieved by vascular bypass surgery gained overall confidence in the procedure.[51,52] Nowadays, peripheral bypass surgery is a commonly accepted and widely applied treatment to improve walking distance, diminish calf pain, improve wound healing, or prevent lower limb amputation.[24] Unfortunately, over time vascular graft failure occurs frequently. In patients with

intermittent claudication approximately a third of the infrainguinal bypasses has occluded within five years and in patients with critical limb ischaemia approximately half of all bypasses.[53-55] The long-term patency rates are higher in venous bypasses than in prosthetic bypasses.[56]
In the early 1960's Charles Dotter developed diagnostic angiography into an interventional treatment of arterial occlusive disease.[57] He was the first to describe successful balloon dilations of stenoses and occlusions in the femoral artery.[58] Since Dotter's pioneering work the endovascular techniques for treating symptomatic PAD evolved rapidly with percutaneous transluminal angioplasty (PTA) now being the preferred choice of treatment in claudicants with infrainguinal occlusive lesions up to 10 cm in length.[24] Successful PTA of lesions longer than 10 cm have been reported as well.[59,60] The 1-, 2-, and 5-year patency rates in claudicants with a stenosis in the femoral artery were 77%, 66%, and 55%, respectively.[61] After PTA of an occlusion the 1-, 2-, and 5-year patency rates were somewhat lower, 65%, 54%, and 42%, respectively.[61] Higher rates were reached after stent placement, especially in patients with critical limb ischaemia.[61] Because of the minimally invasive approach PTA resulted in less postoperative complications and deaths and in a shorter hospital stay than bypass surgery, but it is also known to have lower patency, limb salvage, and survival rates on the long term in comparison with bypass surgery.[62-64]

Antithrombotics and bypass patency

Antithrombotic therapy also improves patency and limb salvage rates after bypass surgery. The Dutch BOA Study demonstrated that oral anticoagulants are most effective in the prevention of venous graft occlusions, whereas aspirin was more effective in preventing non-venous graft occlusions. A similar pattern was seen for limb salvage. Patients with venous grafts who were treated with oral anticoagulants underwent less amputations than those treated with aspirin (HR, 0.71; 95% CI, 0.50 to 1.02), whereas patients with non-venous grafts who were treated with aspirin tended to have less amputations than those treated with oral anticoagulants (HR, 1.32; 95% CI, 0.81 to 2.15). With the greater risk of bleeding of antithrombotic therapy guidelines recommend antiplatelet treatment after infrainguinal bypass surgery to prevent graft occlusion regardless of bypass material, and stress only to apply oral anticoagulants in patients at high risk of bypass occlusion or limb loss.[41]

Prognosis of PAD

Within 1 year after peripheral bypass surgery the lower limb amputation rates ranged from 10% to 25%.[65] Within 5 years 30% to 40% of patients will have had a lower limb amputation, with even higher rates reported in patients with critical limb ischaemia.[53,54] The 5-year mortality rate in patients with PAD approximated 20%, of which two thirds had a cardiovascular cause.[66-68] In patients with symptomatic PAD the risk of a vascular death was at least two times higher than in patients with asymptomatic

PAD.[69] A lower ABI is related to a higher risk of all-cause death, vascular death, and ischaemic events.[70-73] The incidence of myocardial infarction and stroke within 5 years is about 10% and 6%, respectively.[66]

The pronounced morbidity and mortality in PAD patients, together with aging of the population and the increasing prevalence of atherosclerotic risk factors in most developed countries, will most likely lead to a substantial demand on health-care and social-care resources in the foreseeable future.[24] This will require an active and multidisciplinary approach for early detection and all-round treatment of PAD in both primary and secondary care.[74,75] Therefore, it is important to know where current clinical practice falls short and should be improved, and to individualize treatment strategies according to risk stratification for an effective and durable prevention of major adverse events in patients with PAD.

Outline of the thesis

This thesis studies the long-term prognosis of patients with PAD after infrainguinal bypass surgery. As PAD is a systemic disease, its prognosis depends on the status of the whole vascular tree. Therefore, our primary aim was to look beyond the scoop of lower limb complications and focus on cardiac and cerebrovascular complications as well. In the assessment of the long-term course of PAD three subjects were considered: 1) the risk of complications throughout the whole arterial tree, 2) the applied drug treatments for prevention of bypass occlusion and ischaemic events, and 3) the quality of life. A complete vascular follow-up of patients with PAD up to 10 years after they underwent infrainguinal bypass surgery has not been reported before. These follow-up data were used to produce a simple tool to determine a patient's vascular risk. This tool will help physicians to inform patients more accurately about their health prospects 10 years from now and to improve personal treatment strategies for prevention of adverse arterial events.

First**,** a systematic review of the literature was performed to gain insight in the present knowledge on the long-term vascular morbidity and mortality and its determinants in patients after infrainguinal bypass surgery (**Chapter 2**). Second, data on fatal and non-fatal vascular events of nearly 500 patients who had participated in the Dutch BOA Study were recorded over the past 10 years. Herewith we provided a detailed insight in the course of PAD after infrainguinal bypass surgery at long-term follow-up and derived a prediction model for individual risk assessment (**Chapter 3**). In **chapter 4** the current practice of drug treatment and cardiovascular risk management applied in PAD patients after peripheral bypass surgery by vascular surgeons throughout Europe was summarised in an international survey. Subsequently, the drug use over the past decade in a sample of patients originating from the Dutch BOA study was evaluated (**Chapter 5**). **Chapter 6** describes changes in the quality of life over time and the influence of vascular events on the quality of life. Finally, in **chapter 7 and 8** the consequence of bleeding –the main adverse effect of antithrombotic therapy– was

studied in patients from the Dutch BOA Study, and again in a pooled dataset of the Dutch BOA Study and the WAVE Trial. This thesis concludes with a general discussion (**chapter 9**) and a summary in English and Dutch (**chapter 10 and 11**).

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Chapter 2

A systematic review on the long-term prognosis of patients with peripheral arterial disease after infrainguinal bypass surgery

Submitted

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Abstract

Objective
We aimed to determine the long-term prognosis of patients after peripheral bypass surgery by systematic review of the literature.

Summary Background Data
Most pooled analyses concentrate on graft related outcomes. Besides bypass occlusion, patients after peripheral bypass surgery are at high risk of fatal and non-fatal cardiovascular events. However, this risk is highly underestimated and requires more awareness.

Methods
PubMed, Cochrane Library, and EMBASE Only were searched with terms for peripheral arterial disease, infrainguinal bypass surgery, and long-term follow-up. With univariable and multivariable Poisson regression the incidence of non-fatal adverse events, vascular death, and non vascular death was estimated, including their determinants adjusted for age, sex, and critical limb ischaemia.

Results
In total 35 studies with 28,509 person-years of observation were included. The overall incidence of all-cause death was 8.6 (95% confience interval [CI], 8.1 to 9.1), and of vascular death 6.7 (95% CI, 6.2 to 7.2) per 100 person-years, respectively, with the highest incidence seen between the age of 66 and 70 years. The adjusted characteristics associated with an increased incidence of vascular death were a study's midyear beyond 1995, renal failure, prior lower limb interventions, critical limb ischaemia, a prosthetic graft, and a distal anastomosis below the knee. Scarcely reported non-fatal vascular events were not analysed.

Conclusion
The incidence of vascular death in patients after peripheral bypass surgery is nearly thrice the incidence of non vascular death and increased between 1995 and 2005, especially in patients with an advanced stage of peripheral arterial disease or renal failure. Data on non-fatal vascular events were lacking, though assuming patients would especially benefit from preventing these events, more knowledge on their course is considered essential.

Introduction

Peripheral bypass surgery is a commonly used treatment for patients with peripheral arterial disease (PAD) caused by atherosclerosis.[1] However, graft failure and lower limb amputation occur frequently as a result of progressive atherosclerosis.[2] Additionally, patients with PAD are at high risk of fatal and non-fatal cardiovascular and cerebrovascular ischaemic events, as atherosclerosis affects the whole arterial system.[3-5] The long-term risk of death from a cardiovascular cause over a period of 10 years is three to six times higher in patients with PAD compared with patients without PAD.[6] Most pooled analyses studied graft related outcomes[2,7-10] and the effect of different antithrombotic treatments[11-17] in PAD patients after peripheral bypass surgery. To the best of our knowledge, there are no pooled analyses that have studied the long-term prognosis of patients after peripheral bypass surgery including the occurrence of non-fatal ischaemic events. To determine the long-term vascular morbidity and mortality risk in patients with PAD after infrainguinal bypass surgery, a systematic review of the literature was conducted.

Methods

Search strategy

A systematic literature search was performed in three online databases: PubMed, Cochrane Library, and EMBASE Only. The search engines were consulted with topic-specific medical subject headings (MeSH in MEDLINE), keywords, or free text that were combined into adequate search strings with the Boolean operators 'OR' and 'AND'. The topics were: 1) PAD; 2) infrainguinal bypass surgery; and 3) long-term follow-up. The search was limited to articles published after 1989 and written in English, German, and Dutch. Details on the applied search strings are given in Appendix I.

Study selection

All identified citations were screened on title and abstract, and when necessary on full text for compliance with a-priori determined inclusion and exclusion criteria. Duplicate citations in Cochrane Library and EMBASE Only that were previously identified in PubMed were censored. Of the selected studies the related articles were reviewed online and their references searched manually for additional studies. Corresponding authors were contacted to request the full text of their publication in case no full text could be retrieved online.

Selection criteria

Studies eligible for inclusion consisted of adult patients diagnosed with chronic PAD who underwent infrainguinal bypass surgery with either a prosthetic, venous, or a composite graft. Studies including patients under the age of 18 years or with known co-morbidities such as Buerger's disease, vasculitis or other auto-immune related diseases, haemotologic diseases, organ failure requiring organ transplantation, or a substantially shortened life expectancy were excluded. Also, studies with patients treated for indications other than

disabling intermittent claudication or critical limb ischaemia, or patients who received endovascular revascularisation, an extra-anatomic or experimental bypass, such as cryopreserved, lyophilized, heparin bonded, or drug eluting grafts, or xenografts in more than 10% of the total study population were removed from the analysis.
We selected cohort studies, clinical trials, meta-analyses, or systematic reviews that yielded data on at least three of the following outcome measures: patency, limb salvage rates, survival rates or non-fatal or fatal vascular events for a period of at least 5 years after bypass surgery. Studies reporting only on patient's functional outcome or quality of life after peripheral bypass surgery were excluded, as were case reports, commentaries, letters to the editor, and supplements. The inclusion and exclusion criteria are described in more detail in Appendix II.

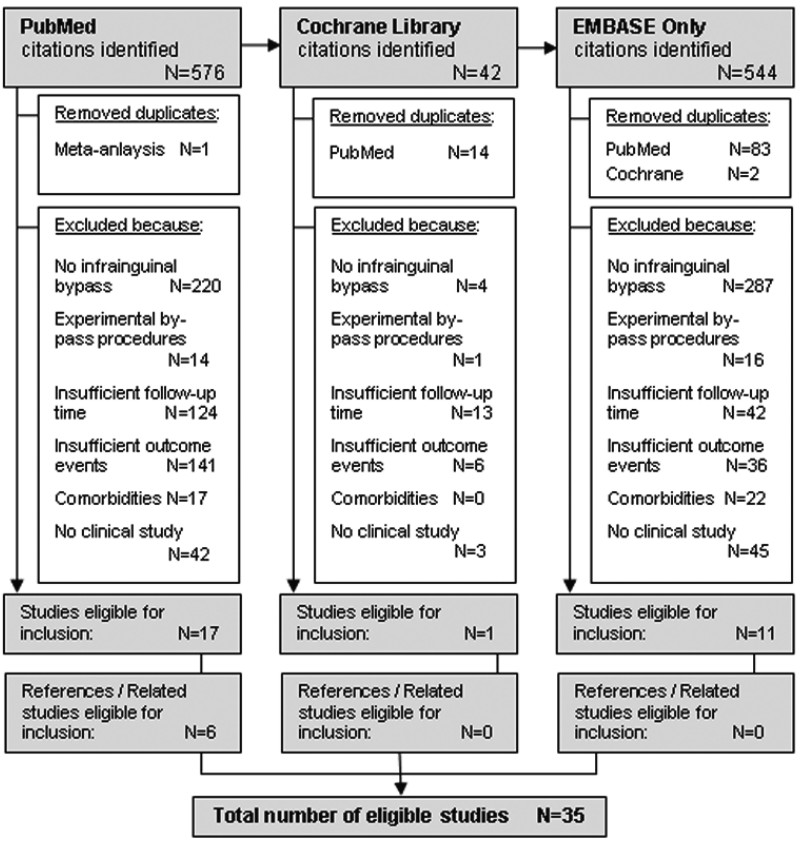
Data abstraction
From the selected studies all relevant data were abstracted with a standard form and entered into a database. Abstracted data consisted of study characteristics, such as study design, study's midyear, level of evidence, demographic facts, patients' cardiovascular risk factors and comorbidities. Further, data on the surgical procedure were collected, including the indication for peripheral bypass surgery, the graft length, and the graft material applied. The recorded outcome measures were patency rates, limb salvage rates, survival rates, late non-fatal ischaemic or hemorrhagic events that occurred beyond 30 days after bypass surgery, and vascular and non-vascular death. Early non-fatal and fatal adverse events that occurred within 30 days of the index bypass procedure were excluded.

Definitions
The clinical diagnosis of intermittent claudication and critical limb ischaemia and outcome measures, such as primary patency rate, assisted primary patency rate, secondary patency rate, limb salvage and late ischaemic or hemorrhagic events were defined in accordance with or highly comparable with the suggested reporting standards of the Ad Hoc Committee of The Society for Vascular Surgery and the North American Chapter of the International Society for Cardiovascular Surgery.[18] The study's midyear was defined as the year halfway the inclusion date of the first patient and the last follow-up date of the last patient. Vascular death was defined as death due to a vascular related event or disease including myocardial infarction, congestive heart failure, arrhythmia, stroke, renal failure, a venous thrombotic event, and major haemorrhage. Sudden death, death of an unknown cause or an unspecified cause was also considered a vascular death. Death from malignancy, infection, trauma or other non-vascular causes were considered a non-vascular death.

Data analysis
Continuous variables are presented with means or medians and discrete variables with frequencies and percentages. The summaries for continuous variables are reported as

weighted means and for discrete variables as totals with percentages.
Patency, limb salvage, and survival rates at 5 year follow-up with their 95% confidence intervals (CI's) are presented as forest plots in order of ascending percentages of patients with critical limb ischaemia. If the study did not report 95% CI's or standard errors, the 95% CI's were computed with Poisson methods.
For each study that provided sufficient data, the incidence of vascular and non vascular death was calculated with corresponding 95% CI's computed with Poisson methods. The overall incidences of vascular and non vascular death with corresponding 95% CI's were estimated with Poisson regression analyses. Univariable Poisson regression analysis was used to assess the incidence of vascular death and non vascular death with corresponding 95% CI's per study characteristic and to determine its possible determinants. In multivariable models possible determinants were adjusted for age, sex, and critical limb ischaemia. Study design, study's midyear, and mean age were incorporated into the models as categorical variables. Other characteristics were incorporated as the proportion of patients with this particular characteristic. Time trend was analysed using the study's midyear.

Figure 1. Literature search including study selection.



Results

Selected studies

The literature search identified a total of 1162 citations. After excluding 99 duplicate citations, 1063 citations remained for study selection. Thirty-six studies met our selection criteria of which one was a meta-analysis that included one of our other selected studies. To prevent repeat inclusion, we excluded the study that was already included in the meta-analysis. Eventually, 35 studies, which consisted of 44 study groups, were eligible for review (Figure 1). These 35 studies were conducted in 11 different countries (Table 1). The majority of these studies were retrospective cohort studies. Five studies were prospective cohort studies, six a randomised clinical trial, and one a meta-analysis. The studies enrolled a total of 8887 patients who underwent a total of 10081 peripheral bypass surgeries and had a mean follow-up of 38 months, resulting in 28509 person-years of observation. Sixty-four percent of patients were male with a mean age of 68 years (Web Table I). Cardiovascular risk factors and co-morbidities that occurred most were hypertension (62%), smoking (55%), diabetes (50%), and coronary artery disease (42%) (Web Table I). Critical limb ischaemia was the main indication for peripheral bypass surgery in 77%. Only 1% of patients required surgical vascular repair for causes other than chronic PAD (e.g. popliteal aneurysm, acute ischaemia, traumatic vascular injury, malignancy, congenital vascular malformations). The majority of patients received a venous femoro-popliteal graft (77%) with a distal anastomosis below the knee (66%). Details on surgical procedures are shown in Web Table II.

Late non-fatal events

At 5-year follow-up, the mean primary patency rate was 58% (95% CI, 56 to 59) as reported in 36 study groups, the mean secondary patency rate was 67% (95% CI, 66 to 69%) as reported in 29 study groups, and the mean limb salvage rate was 79% (95% CI, 77 to 81%) as reported in 32 study groups (Figure 2). At 10-year follow-up, 8 study groups reported a mean primary patency rate of 51% (95% CI, 48 to 54%),and a mean limb salvage rate of 71% (95% CI, 68 to 75%). The mean secondary patency rate at 10-year follow-up was 70% (95% CI, 64 to 75%) as reported in 5 study groups.

Of the late non-fatal adverse events, graft failure occurred most in 28% of patients derived from 26 study groups with a weighted mean follow-up of 55 months (range, 17 to 147) (Table 2). Lower limb amputation occurred in 9% of patients from 29 study groups with a weighted mean follow-up of 56 months (range, 17 to 147). Bleeding occurred in 12% of patients from 3 study groups with a weighted mean follow-up of 35 months (range, 26 to 39). Stroke was reported in 7% of patients from 2 study groups with a weighted mean follow-up of 39 months (range was not reported in the selected studies). Non-fatal myocardial infarction was reported least in 5% of patients from 3 study groups with a weighted mean follow-up of 37 months (range, 33 to 39). Too few late non-fatal adverse events were reported to assess their incidence and determinants.

Table 1. Characteristics of the included studies.

First author	Date start inclusion§	Date stop inclusion§	Study's midyear	Country	Study design	LOE	No. of patients	No. of limbs	Mean FU (months)	No. of PY	Rutherford def. applied	Lost to FU N (%)
Aalders(PTFE)[43]	15.01.83	15.08.84	1984	Netherlands	RC	1b		49	78	319	No	
Watelet[44]												
In situ graft	15.10.80	15.01.85	1985	France	RCT	1b	46	50	146	558	Yes	2 (4)
Reversed graft	15.10.80	15.01.85	1985	France	RCT	1b	45	50	147	551	Yes	1 (2)
Patterson[45]	15.02.79	15.11.87	1987	USA	RC	2b	128	138	22	236	Yes	7 (6)
Quiñones Baldrich[46]	15.12.78	15.12.88	1988	USA	RC	2b	258	322	66	1419	Yes	42 (16)
Kretschmer[47]												
Phenprocoumon	15.06.79	15.12.88	1988	Austria	RCT	1b	66	66	120	660	No	
No phenprocoumon	15.06.79	15.12.88	1988	Austria	RCT	1b	64	64	73	389	No	
El-Massry [48]	15.01.78	15.12.90	1990	USA	RC	2b	154	200	60	764	Yes	
Donaldson[49]	15.03.83	15.06.90	1990	USA	RC	2b	371	440	20	631	No	
Allen[50]												
PTFE graft DA-AK	15.03.87	15.09.93	1993	USA	RC	2b	116	128	51	493	No	
PTFE graft DA-BK	15.03.87	15.09.93	1993	USA	RC	2b	42	45	51	179	No	
Vein graft DA-BK	15.03.87	15.09.93	1993	USA	PC	2b	65	66	51	276	No	
Conte[51]	15.06.77	15.06.93	1993	USA	RC	2b	53	57	32	141	Yes	11 (21)
Belkin[33]												
Males	31.03.83	30.03.93	1993	USA	RC	2b	286	338	30	703	No	25 (9)
Females	31.03.83	30.03.93	1993	USA	RC	2b	204	244	31	524	No	23 (11)
Belkin[52]	01.01.75	01.11.93	1993	USA	RC	2b	251	300	29	607	No	13 (5)
Olojugba[53]	01.07.88	01.07.94	1994	UK	RC	2b	275	299	19‡	435	Yes	
Johnson[54]												
Warfarin + Aspirin	01.10.91	30.09.95	1995	USA	RCT	1b	231	231	39	757	Yes	4 (2)
Aspirin	01.10.91	30.09.95	1995	USA	RCT	1b	227	227	39	743	Yes	10 (4)
Siskin[55]	15.01.92	15.12.95	1995	USA	RC	2b	87	93	20	144	Yes	2 (2)
Cavillon[56]	15.01.84	15.12.95	1995	France	RC	2b	161	162	17	233	Yes	

Table 1 continued First author	Date start inclusion[§]	Date stop inclusion[§]	Study's midyear	Country	Study design	LOE	No. of patients	No. of limbs	Mean FU (months)	No. of PY	Rutherford def. applied	Lost to FU N (%)
Maini[57]	01.01.79	30.06.95	1995	USA	RC	2b	276	338	33	759	Yes	
Devine[58]	15.10.94	15.02.97	1997	UK	RCT	1b		103	76	652	No	
Ballotta[59]												
Calcifications at DA	15.07.90	15.07.97	1997	Italy	RC	2b	65	69	69	374	Yes	0 (0)
No calcifications at DA	15.07.90	15.07.97	1997	Italy	RC	2b	78	83	69	449	Yes	0 (0)
Ballotta[60]	15.01.94	15.12.97	1997	Italy	RCT	1b	51	102	59	251	Yes	0 (0)
Rückert[64]	01.06.92	31.07.98	1998	Germany	RCT	1b	129	135	45	484	No	
Faries[65]	01.01.90	31.08.98	1998	USA	PC	1b	454	520	25	942	Yes	
Chew[66]	15.06.83	15.09.99	1999	USA	RC	2b	154	165	25	321	Yes	13 (20)
Reed[67]	15.01.78	15.09.00	2000	USA	RC	2b	217	249	27	481	Yes	18 (8)
Schneider[68]	01.08.94	31.07.00	2000	USA	RC	2b	110	110	23	211	Yes	
Johansen[69]	15.01.98	15.03.01	2001	USA	PC	1b	92	100	49	376	Yes	
Hertzer[70]	15.07.76	15.12.02	2002	USA	RC	2b	565	650	48[‡]	2260	Yes	
Mori[71]	15.03.82	15.12.02	2002	Germany	RC	2b	215	248	94	1684	Yes	
Chew[72]												
African-Americans	01.01.85	31.12.03	2003	USA	PC	2b	89	89	33	245	Yes	4 (5)
Caucasians	01.01.85	31.12.03	2003	USA	PC	2b	1370	1370	43	4909	Yes	164 (12)
Galaria[73]	15.01.88	15.01.03	2003	USA	RC	2b	87	92	42	305	Yes	
Inoue[74]	15.01.97	15.12.05	2005	Japan	RC	2b	96	99	40	320	Yes	
Varcoe[75]	15.05.97	15.05.05	2005	Australia	PC	1b	35	36	26	76	Yes	
Albers[8]	01.01.87	31.12.05	2005	Brazil	MA	2a	1027	1272	12[‡]	1027	Yes	
Total	-	-	-	-	-	-	8887*	10081*	38[¥]	28509*	32x Yes	380* (9)[θ]

Legend. [§], the median of the month or year were estimated for incomplete dates; LOE, level of evidence (Oxford Centre fro Evidence-based Medicine Levels of Evidence, March 2009); FU, follow-up; PY, person-years; Study design: RCT, randomised clinical trial; PC, prospective cohort study; RC, retrospective cohort study; MA, meta-analysis; PTFE, polytetrafluoroethylene; DA-AK, distal anastomosis above the knee; DA-BK, distal anastomosis below the knee; DA, distal anastomosis; [‡], median follow-up; *, sum of values; [¥], weighted mean of values; [θ], percentage is based on patients in reporting studies only.

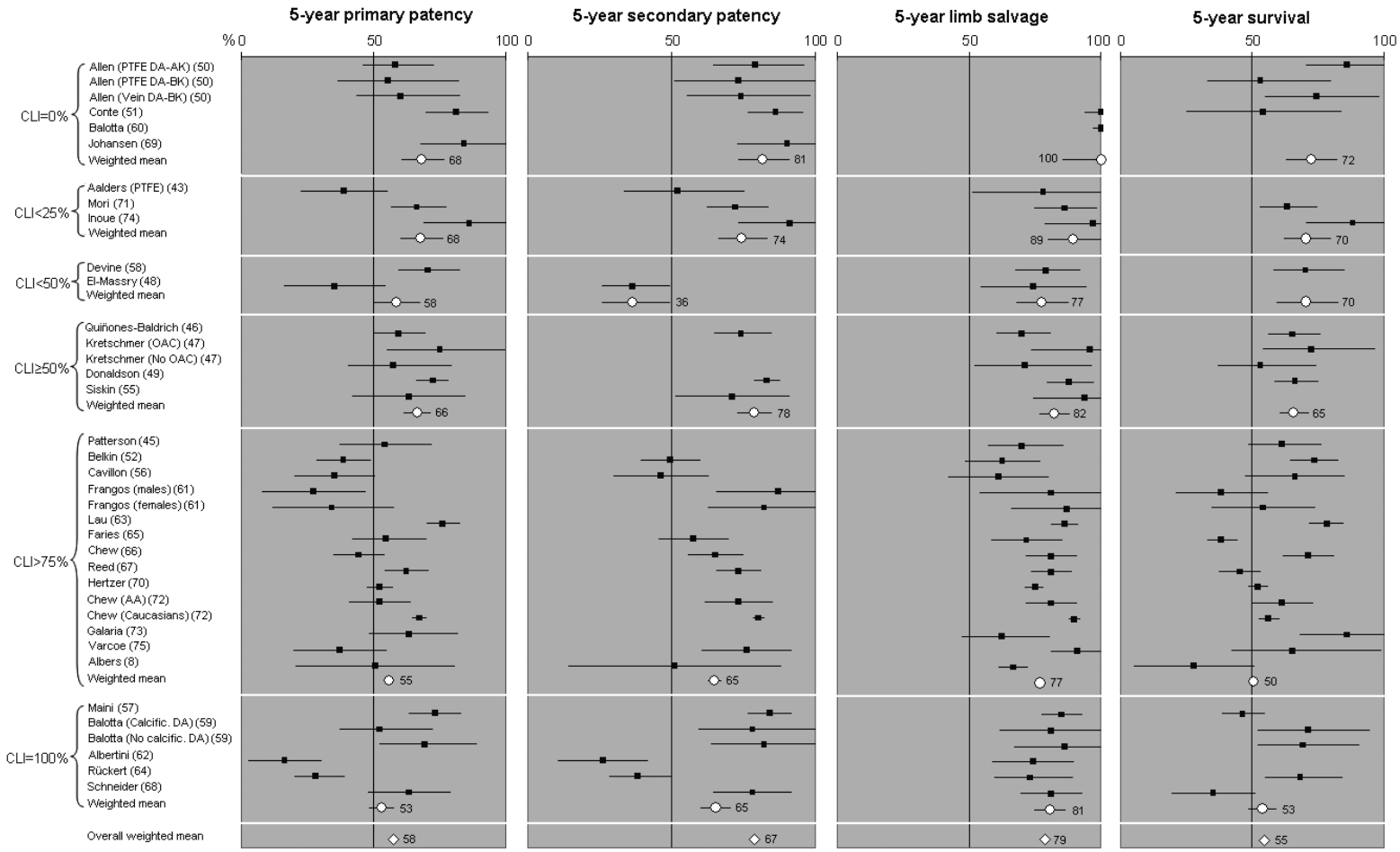

5-year primary patency
5-year secondary patency
5-year limb salvage
5-year survival
% 0
50
100
CLI=0%
Allen (PTFE DA-AK) (50)
Allen (PTFE DA-BK) (50)
Allen (Vein DA-BK) (50)
Conte (51)
Balotta (60)
Johansen (69)
Weighted mean
68
81
100
72
CLI<25%
Aalders (PTFE) (43)
Mori (71)
Inoue (74)
Weighted mean
68
74
89
70
CLI<50%
Devine (58)
El-Massry (48)
Weighted mean
58
36
77
70
CLI≥50%
Quiñones-Baldrich (46)
Kretschmer (OAC) (47)
Kretschmer (No OAC) (47)
Donaldson (49)
Siskin (55)
Weighted mean
66
78
82
65
CLI>75%
Patterson (45)
Belkin (52)
Cavillon (56)
Frangos (males) (61)
Frangos (females) (61)
Lau (63)
Faries (65)
Chew (66)
Reed (67)
Hertzer (70)
Chew (AA) (72)
Chew (Caucasians) (72)
Galaria (73)
Varcoe (75)
Albers (8)
Weighted mean
55
65
77
50
CLI=100%
Maini (57)
Balotta (Calcific. DA) (59)
Balotta (No calcific. DA) (59)
Albertini (62)
Rückert (64)
Schneider (68)
Weighted mean
53
65
81
53
Overall weighted mean
58
67
79
55

Figure 2. Patency, limb salvage, and survival rates with 95% confidence intervals according to increasing percentages of patients with critical limb ischaemia (CLI).

Legend Figure 2. PTFE, polytetrafluoroethylene; DA, distal anastomosis; AK, above the knee; BK, below the knee; OAC, oral anticoagulants; PTA, percutaneous translumincal angioplasty; AA, African-American, Calcific., calcifications.

Long-term mortality

At 5-year follow-up, the mean survival rate was 54% (95% CI, 53 to 56) as reported in 33 study groups, and at 10-year follow-up the mean survival rate of 35% (95% CI, 32 to 38%) as reported in 8 study groups (Figure 2).

The incidence of overall mortality was 8.6 per 100 person-years (95% CI, 8.1 to 9.1) in 26 studies (Table 2). Study characteristics univariably associated with the incidence of overall mortality were study design, a study's midyear, sex, age, hypertension, diabetes, smoking, renal failure, coronary artery disease, prior lower limb interventions, PAD stage, graft material, and graft length (Table 3). When adjusted for age, sex, and critical limb ischaemia, determinants associated with an increased incidence of overall mortality were a study's midyear beyond 1995, female sex (adjusted for age and critical limb ischaemia only), hypertension, diabetes, renal failure, critical limb ischaemia (adjusted for age and sex only), a prosthetic bypass graft, and a distal anastomosis below the knee (Table 4). Determinants that were associated with a decreased incidence of overall mortality were a prospective study design, a randomised clinical trial, a mean age younger than 66 years and older than 70 years (adjusted for sex and critical limb ischaemia only), smoking, coronary artery disease, prior lower limb interventions, intermittent claudication (adjusted for age and sex only), a venous bypass graft, and a distal anastomosis above the knee (Table 4).

The incidence of vascular death was 6.7 per 100 person-years (95% CI, 6.2 to 7.2) in 17 studies (Table 2). Study characteristics univariably associated with the incidence of vascular death were study design, a study's midyear, sex, age, diabetes, renal failure, coronary artery disease, cerebrovascular disease, prior lower limb interventions, PAD stage, graft material, and graft length (Table 3). When adjusted for age, sex, and critical limb ischaemia determinants associated with an increased incidence of vascular death were a study's midyear beyond 1995, renal failure, prior lower limb interventions, critical limb ischaemia (adjusted for age and male sex only), a prosthetic bypass graft, and a distal anastomosis below the knee (Table 4). Determinants that were associated with a decreased incidence of vascular death were a mean age younger than 66 years and older than 70 years (adjusted for sex and critical limb ischaemia only), cerebrovascular disease, intermittent claudication (adjusted for age and sex only), and a venous bypass graft (Table 4).

The incidence of non vascular death was 2.4 per 100 person-years (95% CI, 2.1 to 2.8) in 16 studies (Table 2). Study characteristics univariably associated with the incidence of

non vascular death were a study's midyear, age, hypertension, renal failure, cerebrovascular disease, PAD stage, graft material, and graft length (Table 3). When adjusted for age, sex, and critical limb ischaemia determinants associated with an increased incidence of non vascular death were a study's midyear beyond 1995, hypertension, renal failure, critical limb ischaemia (adjusted for age and sex only), a prosthetic bypass graft, and a distal anastomosis below the knee (Table 4). Determinants that were associated with a decreased incidence of non vascular death were a randomised clinical trial, a mean age between 60 and 65 years (adjusted for sex and critical limb ischaemia only), diabetes, smoking, cerebrovascular disease, intermittent claudication (adjusted for age and sex only), a venous bypass graft, and a distal anastomosis above the knee (Table 4).

	Non-fatal events					Fatal events
First author	Graft failure N (%)	LL amputation N (%)	MI N (%)	Stroke N (%)	Bleeding N (%)	Overall mortality N (%)
Aalders(PTFE)[43]	26 (52)					23 (47)
Watelet[44]						
In situ graft	12 (24)	7 (14)				33 (72)
Reversed graft	7 (14)	7 (14)				31 (69)
Patterson[45]	34 (8)	16 (4)				15 (12)
Quiñones Baldrich[46]	101 (31)	7 (2)				
Kretschmer[47]						
Phenprocoumon	13 (20)	4 (6)				27 (41)
No phenprocoumon	23 (36)	13 (20)				37 (58)
El-Massry [48]		16 (8)				
Donaldson[49]	68 (15)	7 (2)				
Allen[50]						
PTFE graft DA-AK		2 (2)				19 (16)
PTFE graft DA-BK		2 (4)				14 (33)
Vein graft DA-BK		4 (6)				16 (25)
Conte[51]						12 (23)
Johnson[54]						
Warfarin + Aspirin	57 (25)	14 (6)	24 (10)	14 (6)	41 (18)	80 (35)
Aspirin	57 (25)	8 (4)	0 (0)	16 (7)	17 (8)	57 (25)
Siskin[55]		1 (1)				11 (13)
Cavillon[56]	42 (26)	5 (3)				
Maini[57]			11 (4)			
Devine[58]	68 (66)	20 (19)				27 (26)
Ballotta[59]						
Calcifications at DA	9 (13)	12 (17)				19 (29)
No calcifications at DA		10 (10)				24 (13)
Ballotta[60]	11 (11)	0 (0)				5 (10)
Frangos[61]						
Males	22 (18)					29 (29)
Females	13 (14)					16 (19)
Albertini[62]	65 (39)	25 (15)				61 (41)
Lau[63]						47 (15)
Rückert[64]	20 (15)	3 (2)				
Chew[66]	150 (91)	42 (26)				30 (20)
Schneider[68]	21 (19)	9 (8)				
Johansen[69]	12 (12)	0 (0)				2 (2)
Hertzer[70]	175 (27)	107 (16)				406 (72)
Mori[71]	93 (38)	9 (4)				132 (61)
Galaria[73]	34 (37)	35 (38)				
Inoue[74]	10 (10)	2 (2)				8 (0.1)
Varcoe[75]	8 (22)	1 (3)			2 (5)	
Total	1151* (28)[θ]	388* (9)[θ]	35* (5)[θ]	30* (7)[θ]	60* (12)[θ]	1181* (36)[θ]

Table 2. Late non-fatal and fatal events in the included studies.

Legend. LL, lower limb; MI, myocardial infarction; PY, person-years; 95% CI, 95% confidence interval; PTFE, polytetrafluoroethylene; NE, not estimated; DA, distal anastomosis; DA-AK, distal anastomosis above the knee; DA-BK, distal anastomosis below the knee; *, sum of values; θ, percentage is based on patients in reporting studies only; §, overall incidence with 95% CI's estimated with Poisson regression.

Incidence overall mortality per 100 PY (95%CI)	Vascular death N (%)	Incidence vascular death per 100 PY (95%CI)	Non vascular death N (%)	Incidence non vascular death per 100 PY (95%CI)
7.2 (4.6-10.8)	13 (26)	4.1 (2.2-7.0)	10 (20)	3.1 (1.5-5.8)
5.9 (4.1-8.3) 5.6 (3.8-8.0) 6.4 (3.6-10.5)				
4.1 (2.7-6.0) 9.5 (6.7-13.1)	25 (38) 36 (56)	3.8 (2.5-6.6) 9.3 (6.5-12,8)	2 (3) 1 (2)	0.3 (0.0-1.1) 0.3 (0.0-1.4)
3.9 (2.3-6.0) 7.8 (4.3-13.1) 5.8 (3.3-9.4) 8.5 (4.4-14.9)	13 (11) 12 (29) 7 (11) 11 (21)	2.6 (1.4-4.5) 6.7 (3.5-11.7) 2.5 (1.0-5.2) 7.8 (3.9-14.0)	6 (5) 2 (5) 9 (14) 1 (2)	1.2 (0.4-2.6) 1.1 (0.1-4.0) 3.3 (1.5-6.2) 0.7 (0.0-5.6)
10.6 (8.4-13.2) 7.7 (5.8-9.9) 7.6 (3.8-13.7)	49 (21) 38 (17)	6.5 (4.8-8.6) 5.1 (3.6-7.0)	29 (13) 18 (8)	3.8 (1.1-10.2) 3.8 (2.6-5.5)
4.1 (2.7-6.0)				
5.1 (3.1-7.9) 5.3 (3.4-8.0) 2.0 (0.6-4.6)	3 (6)	1.2 (0.2-3.4)	2 (4)	0.8 (0.1-2.9)
18.4 (12.3-26.4) 11.2 (6.4-18.3) 16.0 (12.2-20.5) 5.0 (3.7-6.6)	10 (10) 11 (13) 1 (1) 33 (11)	6.3 (3.0-11.6) 7.7 (3.9-13.9) 0.3 (0.0-1.5) 3.5 (2.4-4.9)	5 (5) 2 (2) 11 (4)	3.2 (1.0-7.4) 1.4 (0.2-5.1) 1.2 (0.6-2.1)
9.3 (6.3-13.3)				
0.5 (0.1-1.9) 18.0 (16.3-20.0) 7.8 (6.6-9.3)	316 (56) 92 (43)	14.0 (12.5-15.6) 5.5 (4.4-6,7)	90 (16) 45 (21)	4.0 (3.2-4.9) 2.7 (1.9-3.6)
2.5 (1.1-4.9)	5 (0.1)	1.6 (0.5-3.6)	3 (0.03)	0.9 (0.2-2.7)
8.6 (8.1-9.1) §	675* (26)θ	6.7 (6.2-7.2) §	236* (10)θ	2.4 (2.1-2.8) §

Table 3. Crude incidence ratios of mortality per study characteristic.

Study characteristics	No. of study groups[§]	Incidence ratio for overall mortality (95% CI)	No. of study groups	Incidence ratio for vascular death (95% CI)	No. of study groups	Incidence ratio for non vascular death (95% CI)
Study design						
Retrospective	15	Ref.	10	Ref.	10	Ref.
Prospective	6	0.46 (0.38-0.55)	2	0.36 (0.22-0.60)	2	0.80 (0.45-1.44)
RCT	4	0.80 (0.69-0.94)	4	0.75 (0.63-0.90)	4	0.74 (0.54-1.02)
Midyear of study						
≤1995	13	Ref.	9	Ref.	9	Ref.
>1995	13	1.41 (1.25-1.59)	8	1.49 (1.26-1.75)	7	1.39 (1.06-1.83)
Sex						
Male	24	0.992 (0.987-0.996)*	15	0.987 (0.981-0.993)*	14	0.999 (0.990-1.009)*
Female	25	1.007 (1.003-1.010)*	15	1.009 (1.004-1.013)*	14	1.001 (0.991-1.010)*
Mean age						
<60	1	0.05 (0.01-0.20)	0	NE	0	NE
60-65	7	0.59 (0.50-0.69)	6	0.58 (0.48-0.71)	6	0.43 (0.30-0.63)
66-70	14	Ref.	9	Ref.	8	Ref.
71-75	4	0.59 (0.51-0.69)	2	0.56 (0.46-0.68)	2	0.67 (0.49-0.91)
>75	0	NE	0	NE	0	NE
Hypertension	23	1.010 (1.006-1.014)*	16	1.002 (0.996-1.007)*	15	1.025 (1.015-1.035)*
Diabetes	26	1.009 (1.005-1.012)*	17	1.018 (1.012-1.024)*	16	0.998 (0.988-1.009)*
Smoking	21	0.981 (0.977-0.986)*	12	1.008 (0.998-1.018)*	11	0.996 (0.979-1.012)*
Renal failure	11	1.058 (1.045-1.071)*	8	1.096 (1.074-1.119)*	7	1.077 (1.043-1.113)*
CAD	19	0.990 (0.985-0.994)*	11	0.977 (0.969-0.986)*	11	0.989 (0.974-1.003)*
CVD	11	0.999 (0.968-1.030)*	7	0.765 (0.666-0.880)*	7	0.794 (0.654-0.964)*
Previous LL intervention	8	1.011 (1.004-1.019)*	5	1.060 (1.039-1.081)*	4	1.030 (0.974-1.089)*
Indication for bypass surgery						
Claudication	21	0.990 (0.988-0.992)*	14	0.986 (0.983-0.988)*	14	0.993 (0.989-0.997)*
CLI	18	1.008 (1.006-1.010)*	10	1.011 (1.008-1.014)*	9	1.006 (1.001-1.012)*
Study graft						
Venous	18	0.991 (0.988-0.994)*	12	0.985 (0.981-0.989)*	11	0.992 (0.985-0.999)*
Prosthetic	14	0.989 (0.987-0.991)*	8	0.985 (0.982-0.988)*	8	0.994 (0.989-0.999)*
DA-AK	17	0.990 (0.988-0.992)*	12	0.989 (0.986-0.991)*	12	0.993 (0.989-0.997)*
DA-BK	19	1.006 (1.004-1.009)*	14	1.006 (1.003-1.009)*	13	1.006 (1.001-1.011)*

Legend. §, Number of included study groups was depended on the availability of sufficient data; 95% CI, 95% confidence interval; RCT, randomised clinical trial; Ref., reference; NE, not estimated; *, incidence

ratio per 1% increase in the percentage of patients with the corresponding study characteristic; CAD, coronary artery disease; CVD, cerebral vascular disease; LL, lower limb; CLI, critical limb ischaemia; DA-AK, distal anastomosis above the knee; DA-BK, distal anastomosis below the knee.

Table 4. Incidence ratio of mortality per study characteristic adjusted for age[¥], sex, and critical limb ischaemia.

Study characteristics	No. of study groups§	Incidence ratio for overall mortality (95%CI)	No. of study groups§	Incidence ratio for vascular death (95%CI)	No. of study groups§	Incidence ratio for non vascular death (95%CI)
Study design						
Retrospective	15	Ref.	10	Ref.	10	Ref.
Prospective	5	0.33 (0.26-0.41)	1	0.35 (0.11-1.11)	1	0.49 (0.12-2.04)
RCT	2	0.38 (0.29-0.51)	2	0.80 (0.61-1.05)	2	0.10 (0.03-0.33)
Midyear of study						
≤1995	23	Ref.	14	Ref.	13	Ref.
>1995	23	1.78 (1.50-2.11)	14	2.07 (1.56-2.75)	13	2.94 (1.66-5.22)
Sex[‡]						
Male	23	0.995 (0.991-1.000)*	14	1.001 (0.994-1.007)*	13	1.002 (0.991-1.013)*
Female	23	1.005 (1.000-1.009)*	14	0.999 (0.993-1.006)*	13	0.998 (0.987-1.009)*
Mean age[¥]						
<60	1	0.08 (0.02-0.32)	0	NE	0	NE
60-65	5	0.64 (0.51-0.80)	4	0.72 (0.55-0.94)	4	0.16 (0.08-0.35)
66-70	13	Ref.	8	Ref.	7	Ref.
71-75	4	0.65 (0.56-0.76)	2	0.64 (0.52-0.80)	2	0.72 (0.51-1.02)
>75	0	NE	0	NE	0	NE
Hypertension	20	1.022 (1.013-1.031)*	13	0.991 (0.997-1.005)*	12	1.043 (1.010-1.078)*
Diabetes	23	1.004 (1.000-1.007)*	14	1.004 (0.996-1.012)*	13	0.970 (0.946-0.995)*
Smoking	20	0.978 (0.973-0.984)*	11	1.004 (0.992-1.016)*	10	0.973 (0.949-0.997)*
Renal failure	11	1.023 (1.009-1.038)*	8	1.029 (1.004-1.055)*	7	1.103 (1.031-1.179)*
CAD	16	0.989 (0.983-0.994)*	8	1.007 (0.989-1.026)*	8	0.994 (0.968-1.021)*
CVD	9	0.983 (0.945-1.023)*	5	0.748 (0.637-0.879)*	5	0.760 (0.577-0.999)*
Previous LL intervention	8	0.988 (0.977-0.999)*	5	1.072 (1.009-1.139)*	4	1.109 (0.983-1.252)*
Indication for bypass surgery[ϕ]						
Claudication	23	0.990 (0.988-0.992)*	14	0.989 (0986-0.992)*	13	0.991 (0.985-0.996)*
CLI	23	1.010 (1.008-1.013)*	14	1.011 (1.008-1.014)*	13	1.009 (1.004-1.015)*
Study graft						
Venous	23	0.997 (0.995-0.999)*	14	0.985 (0.981-0.989)*	13	0.988 (0.981-0.996)*
Prosthetic	23	1.002 (1.000-1.005)*	14	1.015 (1.011-1.020)*	13	1.011 (1.003-1.019)*
DA-AK	21	0.995 (0.993-0.998)*	14	0.997 (0.994-1.000)*	13	0.993 (0.987-0.998)*
DA-BK	20	1.005 (1.002-1.007)*	14	1.003 (1.000-1.006)*	13	1.007 (1.002-1.013)*

Legend Table 4. [¥], With age as a continuous variable; [§] number of included study groups was depended on the availability of sufficient data; 95% CI, 95% confidence interval; RCT, randomised clinical trial; Ref., reference; [‡], only adjusted for age and critical limb ischaemia; *, incidence ratio per 1% increase in the percentage of patients with the corresponding study characteristic; [¥], only adjusted for male sex and critical limb ischaemia; NE, not estimated; CAD, coronary artery disease; CVD, cerebral vascular disease; LL, lowerlimb; [θ], only adjusted for age and male sex; CLI, critical limb ischaemia; DA-AK, distal anastomosis above the knee; DA-BK, distal anastomosis below the knee.

Discussion

Long-term mortality

A systematic review on the long-term morbidity and mortality of patients with PAD after peripheral bypass surgery was performed in 35 studies with 28509 person-years of observation. Our results primarily focused on long-term mortality because not enough non-fatal events were reported to allow for multivariate analyses. Over a mean follow-up of 38 months the all-cause mortality rate was 36% with an incidence of 8.6 per 100 person-years. The highest incidence of overall mortality was seen between the age of 66 and 70 years. In comparison with other studies[19-25], we found a slightly higher overall-mortality rate. Cohort studies in patients with symptomatic leg ischaemia reported 5-year all-cause mortality rates between 14 and 32%.[19-25] However, these percentages were also based on PAD patients who did not receive peripheral bypass surgery. Peripheral bypass surgery is mostly performed in patients with a more advanced stage of PAD (e.g. critical limb ischaemia or a low ankle-brachial index), which is associated with a higher mortality rate.[19,25-28] In 77% of patients in our pooled analyses the indication for bypass surgery was critical limb ischaemia.

Most adjusted study characteristics we found to be associated with the incidence of overall mortality were consistent with independent predictors reported in other studies, such as age older than 65 years, hypertension, diabetes, smoking, renal failure, cardiac disease, and critical limb ischaemia.[19,29,30] However, in contradiction with results in other studies[19,29,30], we found an age older than 70 years, smoking, coronary artery disease, and prior lower limb interventions to decrease the incidence of overall mortality. The decrease in the incidence of overall mortality beyond a certain age might be caused by selection bias due to inclusion of healthier elderly in studies. It may also be a finding by chance as the number of studies including a large proportion of octogenarians was low. A possible explanation for the opposite effects of smoking, coronary artery disease, and prior lower limb interventions could be that patients with these characteristics are identified as high risk patients and therefore more likely to receive adequate secondary medical prevention, such as antithrombotics, statins, and blood pressure lowering drugs. In a large worldwide prospective registry PAD patients who had previously undergone a lower extremity procedure or had atherosclerotic co-morbidities (e.g. coronary artery disease or cerebrovascular disease) were found to receive better risk management than PAD patients without these characteristics, such as encouragement to stop smoking and

blood pressure, glucose, and plasma lipid control according to international guideline recommendations.[31] Unfortunately, in the selected studies of our pooled analysis not enough data on applied drug therapies were reported to allow for reliable analyses of this possible association. Lastly, a statistical issue might explain the less plausible effects of these associated characteristics, as our meta-regression analysis was not based on crude data, but on proportions of patients with a certain characteristic. Other associated characteristics were a study's midyear beyond 1995, female sex, graft material, and graft length. An increased incidence of overall mortality after the year 1995 most likely reflects the clinical consequences of a growing elderly population and an increasing prevalence of atherosclerotic risk factors in the developed countries. Perhaps this finding is caused by an observer bias with studies from the early nineties reporting primarily on graft related outcomes instead of on the long-term fatal and non-fatal systemic consequences in patients with PAD as well. Among females the incidence ratio of overall mortality was higher than among males. Our finding was in agreement with previously reported results[32], but differed from others.[33-35] The latter studies reported no significant differences in long-term mortality rates between males and females, but did show women to be older and have a higher prevalence of critical limb ischaemia than men.[33-36] The Framingham Study found women to lag behind men in the incidence of intermittent claudication by 10 years, but eventually to catch up between the age of 64 and 74 years.[37] It was suggested that without the protective effect of estrogen after menopause, PAD advances rapidly in women at an older age.[36] Indeed in patients with symptomatic limb ischaemia, women in their seventies were found to have a higher incidence of overall mortality (9.0 per 100 person-years) than men at the same age (7.5 per 100 person-years).[25] This might explain the higher incidence ratio of overall mortality we found among females in our pooled cohort with a mean age of 68 years. However, after adjusting for age and critical limb ischaemia the incidence ratio for overall mortality among females remained significantly increased, whereas the adjusted incidence ratio for vascular death among females did not. Therefore, other unidentified factors are presumed to play a role.

We observed a vascular mortality rate of 27%, which largely corresponded with rates reported in other studies ranging between 12 and 31%.[19,22,23,26,27] In accordance with other studies in patients with symptomatic leg ischaemia, the risk of vascular death was found to be at least two times higher than the risk of non vascular death.[22,24,27,38] The reported independent predictors of vascular death, renal failure and critical limb ischaemia, corresponded with the characteristics we found to be associated with a higher incidence of vascular death.[19,27] Additionally, we found graft-related characteristics, such as a prosthetic conduit, a distal anastomosis below the knee, and prior lower limb interventions to significantly increase the incidence of vascular death. Possibly these graft-related characteristics occur more frequently in patients with an advanced stage of PAD who therefore are at higher risk of death. Another likely explanation is that these graft features are prone to complications, such as occlusion and infection leading to surgical interventions or sepsis increasing the risk of death. Furthermore,

we found cerebrovascular disease, an age younger than 66, and an age older than 70 years to be associated with a decreased incidence of vascular death. Again, perhaps selection bias, a more adequate applied secondary prevention strategy in high risk patients, or a statistical issue might explain the effects of these associated characteristics.

Long-term morbidity

Unfortunately, late non-fatal adverse events were hardly reported in the studies we selected. The majority of studies focused on the clinical and technical success of the peripheral bypass procedure, primarily reporting early procedure-related complications and long-term patency, limb salvage, and survival rates only. In the scarce studies that reported myocardial infarctions, strokes, and lower limb amputations we found frequencies of 5%, 7%, and 9%, respectively, which are probably underestimated. Higher percentages were reported in the Edinburgh Artery Study for the occurrence of a stroke or a transient ischaemic attack over 5 years ranging between 3% and 7% in patients with different severities of PAD, and for acute myocardial infarction ranging between 8% and 11%.[24] A study in 397 patients found 14% of patients to have had a major amputation at a mean follow-up of 43 months after infrainguinal bypass surgery.[39] The pooled patency, limb salvage, and survival rates largely corresponded with rates reported by other studies. A meta-analysis of 73 studies reported a 5-year primary and secondary patency rate of 65% and 80%, respectively, for below-knee venous femoropopliteal conduits in claudicants.[2] However, in patients with critical limb ischaemia the reported 5-year primary and secondary patency rates of 69% and 78%, respectively, were substantially higher than our pooled rates of 53% and 65%. Probably, the rates we found were lower because the included patients also received prosthetic conduits instead of venous conduits only. A meta-analysis in patients with polytetrafluoroethylene conduits only showed a 5-year primary and secondary patency rate of, respectively, 31% and 40%.[7] The rates we found are indeed between these reported patency rates of prosthetic and venous conduits. To our knowledge, no meta-analyses or systematic reviews were published on long-term limb salvage after infrainguinal bypass surgery that allow a fair comparison of our reported 5-year limb salvage rates. Only the meta-analysis on polytetrafluoroethylene conduits reported a foot preservation rate of 56% at 5-years follow-up, which is considerably lower than the limb salvage rate of 79% we reported.[7] This difference might be explained by the higher graft failure rate of prosthetic conduits than of venous conduits with a subsequent higher incidence of lower limb amputation.[9,40] Further, we assumed that the definition of foot preservation also included small amputations below the ankle (e.g. toe amputation) that occur more often than major amputations above the ankle. More pooled analyses on long-term limb salvage in PAD patients are needed. Furthermore, no meta-analyses or systematic reviews were found for comparison with our reported 10-year follow-up rates.

Limitations

An inherent limitation of our systematic review is that the meta-regression analysis is based on proportions. Therefore, the effects of associated characteristics should be interpreted with some caution. A pooled analysis with individual data would provide more accurate risk estimates of possible determinants for mortality, however this is hard to accomplish with trials done relatively far back in the past. A second limitation is the poor report on late non-fatal adverse events. Our review was eventually restricted to the evaluation of long-term mortality. Nevertheless, we reported pooled patency and limb salvage rates at 5-year and 10-year follow-up according to the proportion of patients with disabling intermittent claudication and critical limb ischaemia. Herewith, an elaborate and up-to-date overview on long-term procedure-related outcomes was given. Moreover, these procedure-related outcomes not only provide information regarding the procedure's clinical and technical success, but also illustrate a patient's physical functioning over time and therewith the quality of life.[41,42] An impaired health related quality of life seems to be mainly driven by a patient's physical health.[41,42] Of course, cardiovascular and cerebrovascular events have considerable disabling consequences affecting the quality of life as well[41], but more importantly have a high risk of being fatal.[19,20] New insights on the incidence and determinants of long-term mortality will help to better understand the course of the disease, to advance patient information, and to improve risk management strategies that will prevent fatal and non-fatal vascular events in patients with PAD after peripheral bypass surgery.

Conclusion

The incidence of vascular death in patients with PAD after peripheral bypass surgery doubled between 1995 and 2005 and is thrice the incidence of non-vascular death, especially in patients with an advanced stage of peripheral arterial disease or renal failure. The highest mortality rate was seen between the age of 66 and 70 years, irrespective of sex or PAD stage. However, our pooled analysis was primarily based on proportions of study characteristics and should be interpreted with some caution. Pooled analysis with individual data is needed to provide more accurate risk estimates of mortality and its possible determinants. Moreover, additional data on the course non-fatal vascular events is required, assuming that patients would especially benefit from preventing non-fatal vascular events.

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Appendix I. Applied search strings per search engine.

PubMed 1990-2009:
("Arterial Occlusive Diseases"[MeSH] OR "Peripheral Vascular Diseases"[MeSH] OR "atherosclerosis"[Title/Abstract] OR "pad"[Title/Abstract] OR "paod"[Title/Abstract] OR "claudication"[Title/Abstract] OR "peripheral arterial disease"[Title/Abstract] OR "limb ischemia"[Title/Abstract]) AND (("infrainguinal"[Title/Abstract] OR "infra inguinal"[Title/Abstract] OR "lower extremity"[Title/Abstract] OR "femoro*"[Title/Abstract]) AND ("bypass*"[Title/Abstract] OR "revascularization"[Title/Abstract] OR "revascularisation"[Title/Abstract] OR "surgery"[Title/Abstract])) AND ("Prognosis"[MeSH] OR "Follow-Up Studies"[MeSH] OR "prognosis"[Title/Abstract] OR "long term follow up"[Title/Abstract] OR "long term prognosis"[Title/Abstract] OR "long term outcome"[Title/Abstract]) AND (English[lang] OR Dutch[lang] OR German[lang])

Cochrane Library 1990-2009:
(MeSH descriptor Arterial Occlusive Diseases explode all trees or MeSH descriptor Peripheral Vascular Diseases explode all trees or "peripheral arterial disease":ti,ab,kw or (pad):ti,ab,kw or (claudication):ti,ab,kw or "intermittent claudication":ti,ab,kw or "peripheral arterial obstructive disease":ti,ab,kw or (paod):ti,ab,kw or (atherosclerosis):ti,ab,kw or "limb ischemia":ti,ab,kw or "critical limb ischemia":ti,ab,kw or (cli):ti,ab,kw) AND ("infrainguinal bypass":ti,ab,kw or "infra inguinal bypass":ti,ab,kw or "femoropopliteal bypass":ti,ab,kw or "femoro popliteal bypass":ti,ab,kw or "femorodistal bypass":ti,ab,kw or "femoro distal bypass":ti,ab,kw or "femorocrural bypass":ti,ab,kw or "femoro crural bypass":ti,ab,kw or "lower extremity bypass":ti,ab,kw or "lower extremity revascularization":ti,ab,kw) AND (MeSH descriptor Prognosis explode all trees or MeSH descriptor Follow-Up Studies explode all trees or (prognosis):ti,ab,kw or "long term prognosis":ti,ab,kw or "long term results":ti,ab,kw or "long term follow up":ti,ab,kw)

EMBASE Only 1990-2009:
((((‘arteriosclerosis’/exp OR ‘arteriosclerosis’) OR (‘peripheral occlusive artery disease’/exp OR ‘peripheral occlusive artery disease’)) AND (‘femorocrural bypass’ OR ‘femorodistal bypass’ OR ‘infrainguinal bypass’ OR (‘femorotibial bypass’/exp OR ‘femorotibial bypass’) OR (‘femoropopliteal bypass’/exp OR ‘femoropopliteal bypass’) OR (‘limb ischemia’/exp OR ‘limb ischemia’))) AND (‘long term outcome’ OR ‘long term results’ OR (‘follow up’/exp OR ‘follow up’) OR (‘prognosis’/exp OR ‘prognosis’))) AND [embase]/lim AND [english]/lim AND [humans]/lim

Appendix II. Study selection criteria.

Inclusion criteria:

- Participants:
  - Patients 18 years of age or older with chronic PAD.
- Intervention:
  - Indication for intervention was disabling intermittent claudication or critical limb ischaemia presenting with rest pain, ulcers and/or gangrene.
  - Treatment with infrainguinal prosthetic or (autogenous) venous bypass surgery, including conduits conducted from the saphenous veins, the umbilical vein, arm veins and composite vein grafts from previous veins.
- Outcome measures:
  - At least three of the following vascular events must be registered up to a follow-up of at least 5 years with the mean or median follow-up reported: patency, limb salvage, with or without survival rate, and non-fatal or fatal vascular events that occurred beyond 30 days after bypass surgery.
- Study types: cohort studies, clinical trials, meta-analysis, or systematic reviews.

Exclusion criteria:

- Participants:
  - Patients younger than 18 years of age without chronic PAD.
  - Known co-morbidities: Buerger's disease, vasculitis, other auto-immune related diseases, haematologic diseases, substantially shortened life expectancy, or all participants of the cohort underwent organ transplantation.
- Intervention:
  - Indication for intervention other than disabling intermittent claudication or critical limb ischaemia in more than 10% of study population or study limbs: acute ischaemia, popliteal aneurysm, traumatic vascular injury, malignancy, congenital vascular malformations, or other causes requiring surgical vascular repair besides the consequences of chronic PAD.
  - Peripheral bypass grafts with a suprainguinal proximal anastomosis or an extra-anatomic route (e.g. axillo-femoral or femoro-femoral cross over) in more than 10% of the total study population or study limbs.
  - Application of experimental grafts such as cryopreserved, lyophilized, heparin bonded, or drug eluting grafts, or xenografts in more than 10% of the total study population or study limbs were excluded.
  - Peripheral endovascular revascularisation: percutaneous transluminal angioplasty, catheter-directed thrombolysis, thromboendarterectomy, suprainguinal or femoro-femoro crossover bypass procedures experimental.

- Outcome measures:
  - A follow-up of less than 5 years or without the mean or median follow-up reported.
  - Reporting less than 3 of the following outcome measures: patency, limb salvage, survival rate, and non-fatal or fatal vascular events that occurred beyond 30 days after bypass surgery.
  - Reporting only functional outcome or quality of life after peripheral bypass surgery.
- Study types: case reports, commentaries, letters to the editor, or supplements.

Web Table I. Patient characteristics of the included studies.

First author	Male sex N (%)	Mean age (years)	Hypertension N (%)	Hyperlipidaemia N (%)
Aalders(PTFE)[43]		63‡	23 (47)	
Watelet[44]				
In situ graft	40 (87)	68	20 (44)	
Reversed graft	34 (71)	67	25 (56)	
Patterson[45]	95 (74)	63	70 (55)	
Quiñones Baldrich[46]	157 (61)	67	155 (60)	
Kretschmer[47]				
Phenprocoumon	52 (79)	63	18 (27)	
No phenprocoumon	50 (78)	62	17 (27)	
El-Massry[48]	110 (71)	67	94 (61)	
Donaldson[49]	218 (59)	68	223 (60)	
Allen[50]				
PTFE graft DA-AK	73 (63)	66	78 (67)	
PTFE graft DA-BK	32 (76)	65	31 (74)	
Vein graft DA-BK	42 (65)	68	45 (69)	
Conte[51]	44 (83)	66	37 (70)	
Belkin[33]				
Males	286 (100)	67	155 (54)	
Females	0 (0)	71	146 (72)	
Belkin[52]	168 (67)	65	130 (52)	
Olojugba[53]	188 (68)	71‡	103 (37)	
Johnson[54]				
Warfarin + Aspirin	229 (99)	66	209 (91)	
Aspirin	225 (99)	65	202 (89)	
Siskin[55]	57 (66)	67		
Cavillon[56]	110 (68)	69	64 (40)	
Maini[57]	199 (72)	76	168 (61)	
Devine[58]	66 (64)	65	39 (38)	9 (9)
Ballotta[59]				
Calcifications at DA	51 (78)	73	42 (61)	
No calcifications at DA	58 (74)	75	52 (63)	
Ballotta[60]	33 (65)	62	31 (61)	22 (43)
Frangos[61]				
Males	100 (100)	67	69 (69)	8 (8)
Females	0 (0)	69	64 (75)	9 (11)
Albertini[62]	90 (61)	70	96 (65)	20 (13)
Lau[63]	197 (63)	71	183 (58)	26 (8)
Rückert[64]	89 (69)	65	93 (72)	
Faries[65]	286 (63)	69	301 (66)	
Chew[66]	87 (57)	69	95 (62)	
Reed[67]	126 (58)	67	134 (62)	
Schneider[68]	67 (61)	69	88 (80)	
Johansen[69]	62 (67)	59		
Hertzer[70]	358 (63)	66		
Mori[71]	182 (85)	71	140 (65)	105 (49)
Chew[72]				
African-Americans	38 (43)	65‡	74 (83)	
Caucasians	813 (59)	70†	849 (62)	
Galaria[73]	54 (62)	63	64 (74)	52 (60)
Inoue[74]	85 (80)	70	60 (62)	26 (27)
Varcoe[75]	22 (63)	73	26 (74)	20 (57)
Albers[8]	503 (49)	63		
Total	5776* (64)θ	68¥	4513* (62)θ	297* (24)θ

Legend. DM, diabetes mellitus; CAD, coronary artery disease; CVD, cerebrovascular disease; LL interv, lower limb intervention; PTFE, polytetrafluoroethylene; ‡, median age; DA-AK,

DM N (%)	Smoking N (%)	Renal failure N (%)	CAD N (%)	CVD N (%)	Previous LL interv. N (%)
8 (16)	35 (71)		18 (37)		
11 (24)	37 (74)		6 (13)	8 (17)	
8 (18)	33 (73)		10 (22)	4 (9)	
58 (45)	109 (85)		52 (41)		
80 (31)	211 (82)		121 (47)		
23 (35)			17 (26)		
51 (80)			16 (25)		
35 (23)	105 (68)		88 (57)	29 (19)	
142 (38)	229 (62)	19 (5)	160 (43)		31 (8)
40 (35)	68 (59)				
13 (31)	21 (50)				
20 (31)	24 (37)				
13 (25)	31 (58)	3 (6)	23 (43)		8 (15)
107 (37)	172 (60)	19 (7)	141 (49)		22 (8)
93 (46)	104 (51)	12 (6)	82 (40)		17 (8)
85 (34)	192 (76)		118 (47)	14 (6)	28 (9)
84 (31)			70 (25)		
119 (52)			43 (19)	40 (18)	
118 (52)			53 (24)	40 (18)	
32 (36)	46 (52)				
45 (28)	64 (40)	4 (3)	47 (29)		31 (19)
174 (63)	152 (55)	36 (13)	108 (39)		32 (10)
14 (14)	95 (92)		27 (26)		
61 (88)	58 (84)	17 (24)	55 (78)	10 (14)	11 (16)
54 (65)	59 (71)	4 (5)	61 (73)	14 (17)	10 (12)
27 (53)	44 (86)		13 (25)	12 (24)	
56 (56)	65 (65)	14 (14)		17 (17)	45 (37)
49 (58)	44 (52)	15 (18)		14 (16)	29 (31)
52 (35)	46 (31)	26 (18)			12 (7)
141 (45)	217 (69)	7 (2)	111 (35)	60 (19)	
57 (44)	82 (64)	12 (9)	29 (23)		95 (74)
386 (85)	349 (77)	66 (15)	299 (66)		
83 (54)	65 (42)	6 (4)	106 (69)		79 (48)
140 (65)	59 (27)	53 (24)	109 (50)		50 (23)
	30 (27)	34 (31)	61 (55)		27 (25)
24 (26)	82 (89)		32 (35)		
266 (47)		112 (20)	127 (22)		180 (28)
69 (32)	159 (74)	30 (14)	93 (43)	39 (18)	
56 (63)	30 (34)	30 (34)	37 (42)	19 (21)	21 (24)
656 (48)	513 (37)	173 (13)	689 (50)	157 (11)	229 (17)
55 (63)	37 (43)	20 (23)	24 (28)	18 (21)	25 (29)
41 (43)	83 (86)	12 (13)	11 (11)		
24 (40)	21 (60)	6 (17)	13 (37)		16 (43)
822 (80)	401 (39)	1027 (100)			
4492* (50)$^{\theta}$	4172* (55)$^{\theta}$	1757* (26)$^{\theta}$	3070* (42)$^{\theta}$	495* (15)$^{\theta}$	988* (21)$^{\theta}$

distal anastomosis above the knee; DA-BK, distal anastomosis below the knee; DA, distal anastomosis; *, sum of values; $^{\theta}$, percentage is based on patients in reporting studies only.

Web Table II. Procedure characteristics of the included studies.

First author	IC N (%)	CLI N (%)	Rest pain N (%)	Tissue loss N (%)
Aalders(PTFE)43	41 (84)	8 (16)	6 (12)	0 (0)
Watelet[44]				
In situ graft	1 (2)	47 (94)	9 (18)	38 (76)
Reversed graft	1 (2)	46 (92)	9 (18)	37 (74)
Patterson[45]	25 (18)	105 (76)	57 (42)	48 (33)
Quiñones Baldrich[46]	132 (41)	190 (59)	89 (47)	101 (53)
Kretschmer[47]				
Phenprocoumon	32 (48)	34 (52)		
No phenprocoumon	30 (47)	34 (53)		
El-Massry[48]	143 (72)	57 (28)		
Donaldson[49]	141 (32)	299 (68)	148 (34)	151 (34)
Allen[50]				
PTFE graft DA-AK	128 (100)	0 (0)	0 (0)	0 (0)
PTFE graft DA-BK	45 (100)	0 (0)	0 (0)	0 (0)
Vein graft DA-BK	66 (100)	0 (0)	0 (0)	0 (0)
Conte[51]	57 (100)	0 (0)	0 (0)	0 (0)
Belkin[33]				
Males	108 (32)	230 (68)	118 (35)	112 (33)
Females	73 (30)	171 (70)	74 (30)	97 (40)
Belkin[52]	50 (17)	250 (84)	159 (53)	92 (31)
Olojugba[53]	40 (13)	258 (87)		
Johnson[54]				
Warfarin + Aspirin				
Aspirin				
Siskin[55]	33 (36)	60 (64)	21 (22)	39 (42)
Cavillon[56]	0 (0)	150 (93)	55 (34)	95 (59)
Maini[57]	0 (0)	338 (100)	203 (60)‡	
Devine[58]	59 (57)	44 (43)		
Ballotta[59]				
Calcifications at DA	0 (0)	69 (100)	20 (29)	49 (71)
No calcifications at DA	0 (0)	83 (100)	33 (40)	50 (60)
Ballotta[60]	102 (100)	0 (0)	0 (0)	0 (0)
Frangos[61]				
Males	12 (10)	110 (90)	41 (34)	69 (57)
Females	12 (13)	83 (87)	44 (46)	39 (41)
Albertini[62]	0 (0)	165 (100)	54 (33)	111 (67)
Lau[63]	85 (24)	264 (76)	46 (13)	218 (63)
Rückert[64]	0 (0)	135 (100)	65 (48)	0 (0)
Faries[65]	9 (2)	511 (98)	85 (16)	426 (81)
Chew[66]	17 (10)	149 (90)	59 (36)	89 (54)
Reed[67]	19 (8)	230 (92)	56 (23)	174 (69)
Schneider[68]	0 (0)	110 (100)	0 (0)	110 (100)
Johansen[69]	100 (100)	0 (0)	0 (0)	0 (0)
Hertzer[70]	97 (15)	553 (85)	232 (36)‡	305 (47)‡
Mori[71]	194 (78)	54 (22)		
Chew[72]				
African-Americans	8 (9)	81 (91)	28 (32)	53 (60)
Caucasians	267 (20)	1103 (80)	431 (31)	672 (49)
Galaria[73]	15 (16)	72 (78)		
Inoue[74]	80 (81)	19 (19)	5 (5)	14 (14)
Varcoe75	4 (11)	33 (89)		
Albers[8]	0 (0)	1301 (99)	263 (20)	1038 (79)
Total	2226* (23)θ	7446* (77)θ	2410* (28)θ	4207* (51)θ

Legend. IC, intermitting claudication; CLI, critical limb ischaemia; §, Other indications for surgical vascular repair besides the consequences of chronic PAD were popliteal aneurysm, acute ischaemia, traumatic vascular injury, malignancy, and congenital vascular malforma-

Other indication§ N (%)	Prosthetic bypass N (%)	Venous bypass N (%)	PA-AK N (%)	PA-BK N (%)	DA-AK N (%)	DA-BK N (%)
0 (0)	49 (100)	0 (0)	49 (100)	0 (0)	49 (100)	0 (0)
2 (4)	0 (0)	50 (100)	49 (100)	0 (0)	13 (26)	37 (74)
3 (6)	0 (0)	50 (100)	50 (100)	0 (0)	12 (24)	38 (76)
8 (6)	138 (100)	0 (0)	138 (100)	0 (0)	138 (100)	0 (0)
0 (0)	322 (100)	0 (0)	322 (100)	0 (0)	219 (68)	103 (32)
0 (0)	0 (0)	66 (100)	66 (100)	0 (0)	28 (42)	38 (58)
0 (0)	0 (0)	64 (100)	64 9100)	0 (0)	28 (44)	36 (56)
0 (0)	200 (100)	0 (0)	200 (100)	0 (0)	175 (88)	25 (13)
0 (0)	0 (0)	440 (100)	440 (100)	0 (0)	79 (18)	361 (82)
0 (0)	128 (100)	0 (0)	128 (100)	0 (0)	128 (100)	0 (0)
0 (0)	45 (100)	0 (0)	45 (100)	0 (0)	0 (0)	45 (100)
0 (0)	0 (0)	66 (100)	66 (100)	0 (0)	0 (0)	66 (100)
0 (0)	0 (0)	57 (100)	57 (100)	0 (0)	0 (0)	57 (100)
0 (0)	0 (0)	338 (100)	338 (100)	0 (0)	52 (15)	286 (85)
0 (0)	0 (0)	244 (100)	224 (100)	0 (0)	48 (20)	196 (80)
0 (0)	71 (24)	229 (76)	300 (100)	0 (0)	56 (19)	244 (81)
0 (0)	0 (0)	299 (100)	299 (100)	0 (0)	0 (0)	299 (100)
	0 (0)	231 (100)	229 (99)	0 (0)	29 (13)	200 (87)
	0 (0)	227 (100)	224 (99)	0 (0)	60 (3)	164 (72)
0 (0)	22 (24)	72 (77)	93 (100)	0 (0)	22 (24)	
12 (7)	31 (19)	131 (81)	162 (100)	0 (0)	0 (0)	162 (100)
22 (7)‡	5 (2)	325 (96)	338 (100)	0 (0)	155 (46)	183 (54)
0 (0)	103 (100)	0 (0)				
0 (0)	13 (19)	53 (77)	47 (68)	22 (32)	0 (0)	69 (100)
0 (0)	23 (28)	56 (67)	69 (33)	14 (17)	0 (0)	83 (100)
0 (0)	51 (50)	51 (50)	102 (100)	0 (0)	102 (100)	0 (0)
0 (0)	0 (0)	122 (100)	117 (96)	5 (4)	5 (4)	115 (94)
0 (0)	0 (0)	95 (100)	93 (98)	1 (1)	3 (3)	90 (95)
0 (0)	0 (0)	165 (100)	149 (90)	0 (0)	0 (0)	165 (100)
0 (0)	143 (41)	206 (59)	349 (100)	0 (0)	249 (71)	100 (29)
0 (0)	135 (100)	0 (0)	135 (100)	0 (0)	0 (0)	135 (100)
0 (0)	0 (0)	520 (100)	326 (63)	194 (37)	29 (6)	43 (17)
0 (0)	0 (0)	165 (100)	165 (100)	0 (0)	3 (2)	162 (98)
0 (0)	0 (0)	247 (99)	138 (56)	111 (45)	0 (0)	249 (100)
0 (0)	0 (0)	110 (100)	110 (100)	0 (0)	0 (0)	110 (100)
0 (0)	100 (100)	0 (0)	100 (100)	0 (0)		
16 (3)	222 (34)	389 (60)	635 (98)	15 (2)	106 (16)	544 (84)
0 (0)	248 (100)	0 (0)	248 (100)	0 (0)	203 (82)	45 (18)
0 (0)	0 (0)	89 (100)	89 (100)	0 (0)	29 (33)	60 (67)
0 (0)	0 (0)	1370 (100)	1370 (100)	0 (0)	536 (39)	834 (61)
6 (6)	6 (7)	86 (93)	68 (74)	24 (26)	0 (0)	92 (100)
0 (0)	99 (100)	0 (0)	99 (100)			99 (100)
0 (0)	0 (0)	37 (100)	29 (79)	6 (16)	3 (8)	34 (92)
13 (1)	197 (15)	1117 (85)	1285 (98)	0 (0)	405 (31)	901 (69)
82* (1)θ	2351* (23)θ	7767* (77)θ	9604* (96)θ	392* (4)θ	2964* (30)θ	6470* (66)θ

tions; ‡, multiple indications per patient were applicable; PTFE, polytetrafluoroethylene; PA-AK, proximal anastomosis above the knee; PA-BK, proximal anastomosis below the knee; DA-AK, distal anastomosis above the knee; DA-BK, distal anastomosis below the knee; DA, distal anastomosis; *, sum of values; θ, percentage is based on patients in reporting studies only.

Chapter 3

Long-term risk of vascular events after peripheral bypass surgery: a cohort study

Submitted

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Abstract

Introduction
Patients with peripheral arterial disease (PAD) are at high risk of major ischaemic events in general (including heart and brain). However, long-term data of patients after peripheral bypass surgery are scarce. Our objective was therefore to study the long-term prognosis of patients after peripheral bypass surgery and develop a prediction model which quantifies the long-term risk of ischaemic events.

Methods
We conducted a retrospective cohort study in patients from the Dutch Bypass and Oral anticoagulants or Aspirin (BOA) Study; a multicentre randomised trial comparing oral anticoagulants with aspirin after infrainguinal bypass surgery. The primary outcome was the composite event of non-fatal myocardial infarction, non-fatal ischaemic stroke, major amputation, and vascular death. Cumulative risks were assessed by Kaplan-Meier analysis and independent determinants by multivariable Cox regression models.

Results
From 1995 until 2009, 482 patients were followed for a mean period of 7 years. Follow-up was complete in 94%. The cumulative risk of the primary outcome was 11% at 1 year (95% confidence interval [CI], 9 to 14), 35% at 5 years (95% CI, 31 to 40), and 54% at 10 years (95% CI, 50 to 59). From four independent determinants: age, diabetes, critical limb ischaemia, and prior vascular interventions, we developed a risk chart, which systematically classifies the 10-year risks of the primary outcome event, ranging from 25% to 85%.

Conclusion
This study provided a detailed insight in the course of PAD long after peripheral bypass surgery and enables individual risk assessment of major fatal and non-fatal ischaemic events by means of a risk chart.

Introduction

Infrainguinal bypass surgery is a commonly accepted treatment for critical limb ischaemia (CLI), a grave condition of chronic peripheral arterial disease (PAD).[1] Unfortunately vascular graft procedures frequently fail.[2] Within five years approximately half of the bypasses have failed and 20% to 30% of the patients face a lower limb amputation.[3-5] To improve patency and limb-salvage rates, antithrombotic therapy is applied postoperatively.[6,7] Antithrombotic therapy can also prevent other fatal and non-fatal ischaemic events, such as myocardial infarction and stroke, for which patients with PAD are prone as well.[8-12] Compared with patients with coronary artery disease (CAD) or cerebrovascular disease (CVD), patients with PAD have the highest risk of vascular death and the second highest risk of myocardial infarction and stroke.[12,13] Long-term data of these ischaemic events in PAD patients are scarce and even lacking for patients with severe PAD, such as rest pain, ulceration, or gangrene. The only trial with more than 10-year follow-up after bypass surgery in 155 patients with disabling intermittent claudication that reported not only on lower limb related complications, but on cardiovascular and cerbrovascular events as well started in 1958.[14] These event and survival rates are unlikely to be applicable more than 50 years later. Our objective was therefore to study the long-term prognosis of patients after infrainguinal bypass surgery and to develop a prediction model, which will identify determinants and quantify the long-term risk of ischaemic events in patients with PAD. To this end, the follow-up of patients who participated in the Dutch Bypass and Oral anticoagulants or Aspirin (BOA) Study[10] was extended to more than 10 years. The prediction model should allow a better understanding of the course of the disease and provide individual risk estimates. Personal risk profiles might help the physician to specify the patient information about the extent of their disease and health prospects, and consequently apply a patient-specific targeted treatment for secondary prevention.

Methods

Patients

The present longitudinal cohort study is based on the Dutch BOA Study[10]. Full details of the Dutch BOA Study have been published elsewhere[10], and are briefly summarised here. From 1995 until 1998, a total of 2650 patients was included from 77 medical centres throughout the Netherlands after infrainguinal bypass surgery. To study the effects of oral anticoagulants and aspirin in preventing bypass occlusion, lower limb amputation, and ischaemic events, these patients were randomly allocated to oral anticoagulation (target international normalized ratio [INR] 3.0-4.5) or to aspirin (100 mg carbasalate calcium daily).

For the present long-term follow-up study we used a subset of the patients from the Dutch BOA Study. Six of the 77 Dutch hospitals previously involved in the Dutch BOA Study were selected because they contributed a large proportion of patients in

the study (18%, n=482). The Ethics Committee of the University Medical Centre Utrecht approved the follow-up study.

Data collection

During the BOA Study, follow-up visits took place at 3 and 6 months after surgery and every 6 months thereafter which allowed prospective registration of outcome events. For the subsequent long-term follow-up of the BOA Study, outcome events and drug use of patients who were still alive at their last folow-up visit in April 1998 were collected until August 2009 in a stepwise manner. This methodology is according the proven effective method of the LiLAC Study[15], which investigated the long-term follow-up of patients from the Dutch TIA Trial[16]. First, follow-up data were obtained from the study record and from the patients' attending vascular surgeon. Second, the patients' general practitioner was approached for similar information if data from the vascular surgeon were incomplete. Third, the patient was interviewed about the occurrence of outcome events if data remained incomplete at the general practitioner. In case the patient had died, relatives or acquaintances were approached for follow-up data. If the patient had moved, the last known residence was looked up at the municipality register to trace the patient's new home address. If the patient or their relatives or acquaintances did not respond, the registry office was contacted to inquire whether the patient had died and when.

To confirm a reported outcome event, clinical data specific for that event were gathered from the attending specialist (e.g. discharge letters, laboratory reports, 12-lead electrocardiogram, reports of Doppler or duplex scans, brain scan reports, operation reports, autopsy reports). All participating patients alive at time of our approach gave informed consent on completing our follow-up data.

Outcome events

The primary outcome event was the composite of vascular death, non-fatal myocardial infarction, non-fatal ischaemic stroke, or major lower limb amputation (whichever occurred first). Secondary outcome events were death from a vascular cause; death from a non vascular cause; myocardial infarction; ischaemic stroke; bypass occlusion; major lower limb amputation; and major bleeding. The definitions of the outcome events are summarized in Appendix I. Each recorded outcome event was adjudicated and classified according to the prespecified definitions by a panel consisting of a vascular surgeon, a clinical epidemiologist, a neurologist, and a cardiologist. Discrepancies were resolved by discussion and documented in a logbook to ensure consistent adjudication of the outcome events.

Statistical analyses

Population size

The number of patients selected for the long-term follow-up of the Dutch BOA Study was based on the event rate in the Dutch BOA Study. The event rate of the primary

outcome in the trial was 11.5% per year. At an extended mean follow up of approximately 7 years, we expected 285 of the 482 patients to have had a primary outcome event. The number of 285 anticipated primary outcome events was sufficiently large to allow for the development of prediction models, based on the rule of thumb that 10 outcome events are required to fit one variable into a multivariable model.[17,18]

Basic analyses

Continuous variables were summarised as means, and discrete variables were summarised as frequencies and percentages. Any missing data were imputed with single linear regression analysis. The cumulative risk of mortality and vascular events with 95% confidence intervals (CI) was estimated with Kaplan-Meier analysis and presented graphically as Kaplan-Meier curves. Patient cumulative mortality rates were set off against the average cumulative mortality rates of the Dutch population in the same age category in Kaplan-Meier curves. Data on the mortality in the general Dutch population between 1995 and 2009 were provided by the Central Bureau of Statistics, The Hague/Heerlen, the Netherlands (http://www.statline.cbs.nl/statweb/).
Actual annual risks of the primary composite outcome event, primary bypass occlusion, and primary major amputation of the index limb were calculated from Kaplan-Meier data for subsequent periods of 1 year and presented graphically as smoothed hazard curves.

Prediction model

Risk-factor assessment was performed with the Cox proportional hazards model and reported as hazard ratios (HR) with corresponding 95% CI's. Associated variables that yielded a P value <0.20 in the univariable analysis were grouped according to the order in which information generally becomes available in clinical practice: 1) demographic factors, 2) medical history, and 3) characteristics of peripheral bypass surgery. Subsequently three consecutive multivariable backward stepwise elimination models were set up to identify independent predictors of the primary outcome event per model (significance criteria 0.25 for entry, 0.05 for removal). To prevent overfitting of our models, the regression coefficients were decreased with a uniform shrinkage factor.[19]
The area under the receiver-operator characteristics (AUC-ROC) curves was used to assess the discriminatory performance of the three models. On the basis of independent predictors from the model with the highest discriminatory value, we developed a risk chart to display the 10-year risks for the primary composite outcome event in patients with or without these predictors.

Results

Patients and outcome events

The mean age at study entry was 69 years (range, 31 to 92; standard deviation [SD], 10). The patients' baseline characteristics are summarised in Table 1. The mean follow-

up was seven years (range, 2 days to 14 years; SD, 4 years), accounting for 3374 patient-years. All patients had a complete follow-up until the last patient visit of the Dutch BOA Study. Since then four patients (1%) were completely lost to follow-up. In 28 patients (6%) follow-up data were partly missing, because only the date of death was available without any other information, or the date of last follow-up was before the end of our study.

The primary outcome event occurred in 60% of patients (n=287; Table 2). The cumulative risk of the primary outcome event was 11% (95% CI, 9 to14) at one year, 35% (95% CI, 31 to 40) at five years, and 54% (95% CI, 50 to 59) at ten years (Table 3, Figure 1A). The mean annual risk of the primary outcome event was 8.3% (95% CI, 7.3 to 9.3).

Table 1. Baseline characteristics among patients who experienced the primary outcome event and patients who did not with corresponding hazard ratios and 95% confidence intervals.

Baseline characteristics	Primary outcome present (n=287)	Primary outcome absent (n=195)	Hazard ratio (95% CI)
Demographic characteristics			
Male sex	175 (61%)	138 (71%)	0.8 (0.6-1.0)
Age >69 years	192 (67%)	82 (42%)	2.4 (1.8-3.0)
Age (mean, SD)	71 (9)	66 (10)	1.06 (1.04-1.07)*
Medical History			
Angina pectoris	48 (17%)	32 (16%)	1.0 (0.7-1.4)
Myocardial infarction	51 (18%)	24 (12%)	1.4 (1.0-1.9)
TIA and/or stroke	33 (12%)	16 (8%)	1.5 (1.1-2.2)
ABI (mean, SD)	0.56 (0.41)	0.56 (0.30)	0.89 (0.61-1.30)*
ABI ≤0.9	269 (94%)	181 (93%)	0.9 (0.6-1.5)
ABI ≤0.6	176 (61%)	112 (57%)	1.3 (0.9-1.6)
Critical limb ischaemia	151 (53%)	69 (35%)	2.2 (1.7-2.8)
Diabetes mellitus	78 (27%)	31 (16%)	1.7 (1.3-2.2)
Hypertension	120 (42%)	66 (34%)	1.3 (0.9-1.6)
Hyperlipidaemia	53 (19%)	48 (25%)	0.7 (0.5-1.0)
Smoking	164 (57%)	125 (64%)	0.8 (0.6-1.0)
Vascular intervention	132 (46%)	81 (42%)	1.2 (0.9-1.6)
Trial Bypass			
Femoro-crural/pedal bypass	73 (25%)	34 (17%)	1.7 (1.3-2.2)
Venous bypass	194 (68%)	119 (61%)	1.2 (0.9-1.6)
Trial Medication			
Oral anticoagulants	134 (47%)	105 (54%)	0.9 (0.7-1.2)

Legend. Data are number (%) unless otherwise indicated; *, HR for age or ankle brachial index was based on these characteristics as a continuous variable; TIA, transient ischaemic attack; ABI, ankle-brachial index.

During the first eight years the annual risk of the primary outcome event gradually increased from about 8% to 9% (Figure 2).

The secondary outcome events are listed in Table 2 including the number of repetitive

non-fatal events. During the complete follow-up period all-cause death, vascular or non vascular, occurred in 67% of patients; so including events that occurred beyond 10 years of follow-up. The cumulative risk of all-cause death at one year was 6% (95% CI, 4 to 8), at five years 33% (95% CI, 29 to 37), and at ten years 60% (95% CI, 56 to 64; Table 3 and Figure 1B). Vascular death occurred in 44% of patients. Only 6% died from complications related to their PAD, the majority died from other cardiovascular causes. The cumulative risk of vascular death at one year was 5% (95% CI, 3 to 7), at five years 23% (95% CI, 19 to 27), and at ten years 40% (95% CI, 35 to 45; Table 3 and Figure 1C). Non vascular death occurred in 22% of patients. The cumulative risk of non vascular death at one year was 1% (95% CI, 0.2 to 2), at five years 10% (95% CI, 7 to 13), and at ten years 20% (95% CI, 15.0 to 25; Table 3 and Figure 1D). The cumulative incidences of death and the primary composite outcome event for patients with intermittent claudication or critical limb ischaemia are summarised in Table 3. For the annual risks of vascular death, nonvascular death, and myocardial infarction the same trend was seen as for the annual risks of the primary outcome event (Figure 2). The annual risk for vascular death increased gradually over time from about 5% to 6%, for non vascular death from 2% to 4%, and for myocardial infarction from about 1.5% to 2.5%. The annual risk of bypass occlusion decreased in the first five years from about 6% to 2% for later years. The hazards for major amputation and ischaemic stroke remained fairly constant over time, around 1%.

Table 2. Primary and secondary outcome events.

Outcome events	First events (n=482)
Primary outcome*	287 (60%)
-major amputations	57 (12%)
-non-fatal myocardial infarction	49 (10%)
-non-fatal ischaemic stroke	38 (8%)
-vascular death	143 (30%)
Secondary outcomes:	
-primary bypass occlusion	140 (29%)
-major amputations	59 (12%)
-myocardial infarction	66 (14%)
-ischaemic stroke	50 (10%)
-vascular death	214 (44%)
cardiovascular	63 (29%)
cerebrovascular	24 (11%)
complications related to PAD	12 (6%)
sudden death	43 (20%)
fatal bleeding**	15 (7%)
other	57 (27%)
-non vascular death	107 (22%)
malignancy	59 (55%)
infection	25 (23%)
unnatural death	1 (1%)
other	22 (21%)
-bleeding	71 (15%)***
major bleeding	66 (89%)
minor bleeding	8 (11%)
No outcome events	75 (16%)

Legend Table 2. *, Primary outcome event is the composite of vascular death, non-fatal myocardial infarction, non-fatal ischaemic stroke, and major amputation. **, Fatal bleeding includes intracranial bleeding (e.g. haemorrhagic stroke). ***, Three patients had a major and a minor bleeding; the 71 bleedings represent all first bleedings, either major or minor.

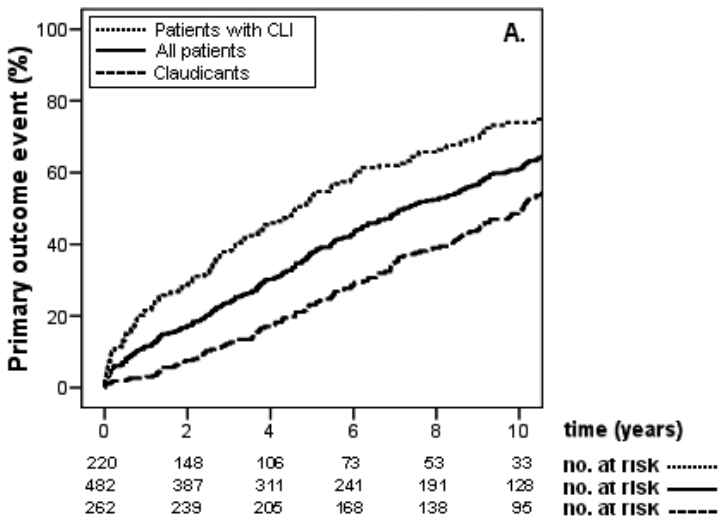
Prediction models

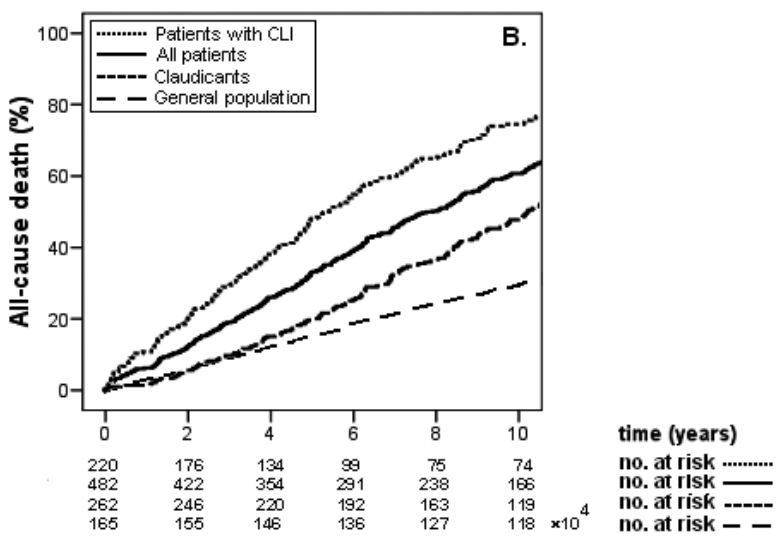
Baseline characteristics associated with the primary outcome event in a univariable model were increasing age, diabetes, critical limb ischaemia, previous myocardial infarction, previous transient ischaemic attack or stroke, and femoro-crural or femoropedal bypass (Table 1). These characteristics all increased the risk of the primary outcome event.

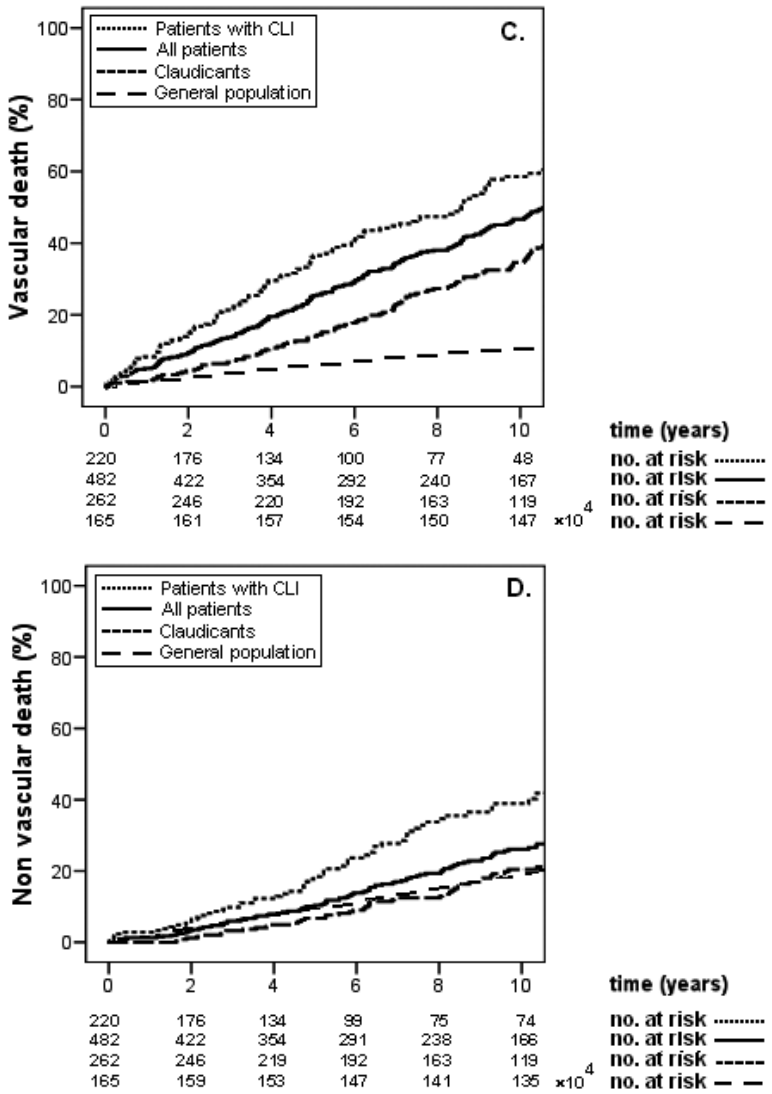
The independent predictors of the primary outcome event, derived from a multivariable model after shrinkage with only minimal changes of the corresponding ß-coefficients, were increasing age, diabetes, critical limb ischaemia, a previous vascular intervention, and construction of a femoro-crural or femoro-pedal bypass (Table 4).

The AUC-ROC curve for the three consecutive prediction models for the primary outcome event were 65%, 68%, and 68%, respectively. The first model was based on age only. The second model had the patient's medical history added, including critical limb ischaemia, diabetes, and a prior vascular intervention. In the third model the length of the applied bypass was added. Because the second model had the same discriminatory performance as the third model we developed the BOA Risk Chart on basis of the second model. Figure 3 systematically displays the 10-year predicted risks of the primary composite outcome event for each combination of the four predictors from model 2. These risks ranged from 25% for a patient younger than 65 years of age with intermittent claudication, no diabetes, and no prior vascular intervention to 85% for a patient older than 75 years of age with critical limb ischaemia, diabetes, and a prior vascular intervention.

Figure 1. Kaplan-Meier estimates of the cumulative incidence of the primary outcome event in all patients, in patients with critical limb ischaemia (CLI), and in patients with intermittent claudication (A); all-cause death in all patients, in patients with CLI, in patients with intermittent claudication, and in the general Dutch population (B); vascular death in all patients, in patients with CLI, in patients with intermittent claudication, and in the general Dutch population (C); and non vascular death in all patients, in patients with CLI, in patients with intermittent claudication, and in the general Dutch population (D).







Legend Figure 1. The number of deaths in the Dutch population are represented as a cumulative percentage instead of a Kaplan-Meier curve.

Table 3. The cumulative incidences of the primary composite outcome event and death at one, five, and ten years with corresponding 95% confidence intervals (95% CI) for patients with intermittent claudication and patients with critical limb ischaemia diagnosed at BOA study-entry.

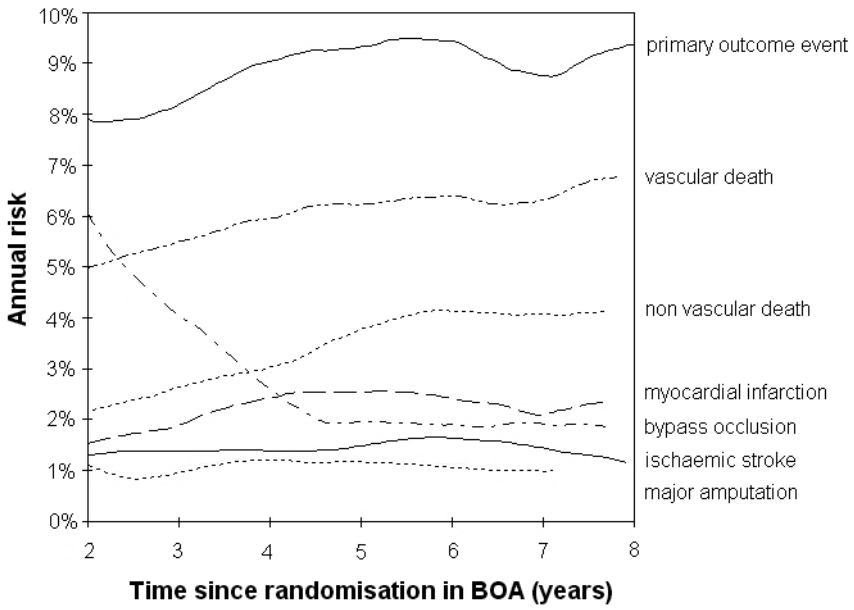
	Cumulative incidence (95% CI)		
Outcome event	1 year	5 years	10 years
Primary composite outcome event in all patients	11 (9-14)	35 (31-40)	54 (50-59)
Intermittent claudication	3 (1-5)	23 (17-28)	45 (38-51)
Critical limb ischaemia	21 (16-27)	51 (44-57)	66 (59-72)
All-cause death in all patients	6 (4-8)	32 (29-37)	60 (55-64)
Intermittent claudication	2 (0.3-4)	20 (15-25)	48 (42-54)
Critical limb ischaemia	11 (7-16)	48 (42-55)	75 (69-80)
Vascular death in all patients	5 (3-7)	23 (19-27)	40 (35-45)
Intermittent claudication	2 (0.3-4)	14 (10-18)	32 (25-38)
Critical limb ischaemia	21 (16-27)	51 (44-57)	66 (59-72)
Non vascular death in all patients	1 (0.2-2)	10 (7-13)	20 (15-25)
Intermittent claudication	0	6 (3-9)	16 (10-22)
Critical limb ischaemia	3 (1-5)	15 (9-20)	26 (17-34)

Discussion

This study provides a ten-year follow-up of 482 patients with peripheral artery disease and infrainguinal bypass surgery and provides a prediction model for individual risk assessment of major ischaemic events at long-term follow-up. Ten years after peripheral bypass surgery more than half of the patients had experienced either a non-fatal myocardial infarct, a non-fatal ischaemic stroke, a major amputation, or had died from a vascular cause. In patients with critical limb ischaemia the risk of an ischaemic outcome event was about two times higher than in patients with intermittent claudication. Interestingly, only six percent died from causes directly related to peripheral atherosclerotic disease, such as lower limb necrosis, infections, or complications from amputations.

Few studies have described both long-term cardiovascular morbidity and mortality in patients after peripheral bypass surgery. One comparable study in 155 patients with intermittent claudication who underwent infrainguinal bypass surgery between 1958 and 1988, reported cumulative all-cause mortality rates of 18% at five years, 34% at 10 years, 45% at 15 years, and 64% at 20 years of follow-up.[14]

Figure 2. Development of the annual risks of the primary composite outcome event and the secondary outcome events.



The 5- and 10-year all-cause mortality rates in patients with intermittent claudication in the Dutch BOA Follow-up Study were higher at 20% and 48%, respectively. Conversely, the reported overall percentage of vascular death and the cumulative incidences of non-fatal myocardial infarction and non-fatal stroke in our study.[20,21] Possibly, we adjudicated more deaths as a vascular cause, because we considered sudden death, death without clear data on its cause, and fatal infections with its primary focus directly related to a previously manifest PAD (e.g. infected ulcer or gangrene, aspiration pneumonia due to dysphagia after stroke) to have a vascular origin. The higher proportions of fatal and non-fatal outcome events in the BOA Follow-up Study may also be explained by the study population's mean age that was 11 years higher. In comparison with another younger and smaller Dutch study cohort, the cumulative all-cause mortality rates were more alike, as well as the proportions of vascular death and non-fatal ischaemic events.[20,21] Apart from age differences and the lower number of patients, the previous study started more than 50 years ago and likely provides now out-dated results.[20,21]

The independent predictors we found for the composite primary outcome event of vascular death, non-fatal myocardial infarction, non-fatal ischaemic stroke, or major lower limb amputation, were increasing age, diabetes, a history of vascular intervention, critical limb ischaemia, and a femoro-crural or femoro-pedal bypass.

Table 4. Indicator variables retained in Cox regression models for prediction of the primary outcome event.

	Model 1* HR (95% CI)	Model 2* HR (95% CI)	Model 3* HR (95% CI)
Demographic facts			
Age**	1.06 (1.04-1.07)	1.05 (1.04-1.07)	1.05 (1.04-1.07)
Medical history			
Critical limb ischaemia	-	1.7 (1.3-2.2)	1.5 (1.2-2.0)
Diabetes mellitus	-	1.5 (1.2-2.0)	1.5 (1.2-2.0)
Vascular intervention	-	1.4 (1.1-1.7)	1.4 (1.1-1.7)
Bypass characteristics			
Femoro-crural/pedal	-	-	1.3 (1.0-1.8)
ROC-AUC (95% CI)	0.65 (0.60-0.70)	0.68 (0.63-0.73)	0.68 (0.63-0.73)

Legend. *, Models after shrinkage. **, Age was taken as a continuous variable with the hazard ratio (HR) representing the risk per year increase.

These independent predictors corresponded largely with those reported in other studies.[14,21] In the BOA Follow-up Study, both hypertension and a history of myocardial infarction were associated with the composite outcome event, but did not reach statistical significance in the multivariable analysis. Possibly, inclusion of major amputations in our composite outcome event led to more PAD-related predictors, such as a history of vascular intervention -most of which were in the peripheral vascular tree-, critical limb ischaemia, and application of a femoro-crural or femoro-pedal bypass. A recent study that developed an index for prediction of amputation free survival in patients with critical limb ischaemia after peripheral bypass surgery identified critical limb ischaemia with tissue loss as an independent predictor (HR, 2.2; 95% CI, 1.4 to 3.4).[22] Because major amputation is a frequent event after infrainguinal bypass surgery,[22] and has the most negative impact on the patient's quality of life of all ischaemic events, we believe major amputation should be included in the primary outcome event in prognostic studies after peripheral bypass surgery.

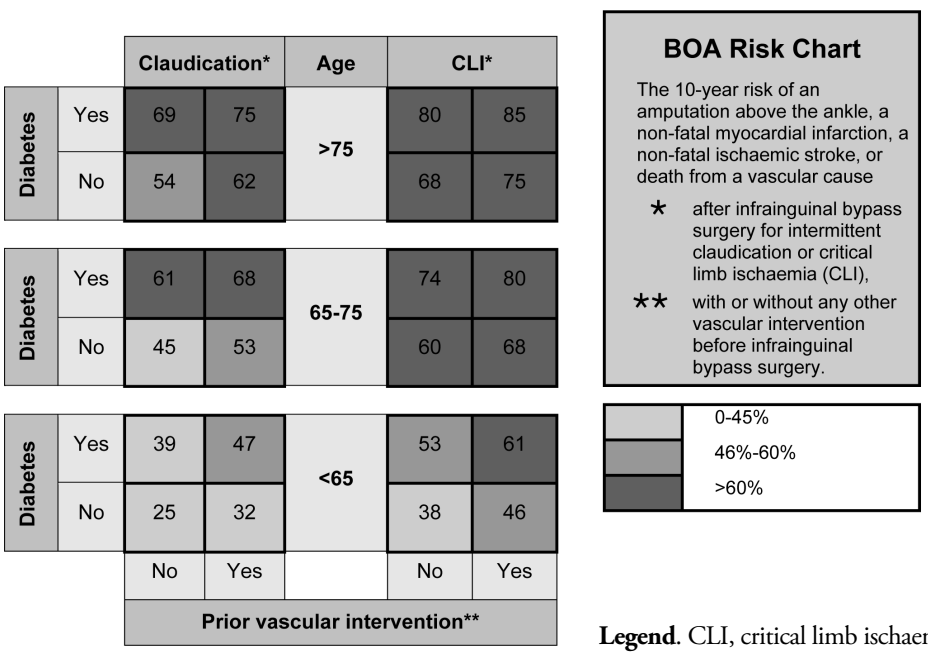
On the basis of four independent predictors of the primary outcome event we developed the BOA Risk Chart. This chart systematically displays the 10-year risks of the primary composite outcome event for patients with or without these four independent predictors after they underwent infrainguinal bypass surgery. For example, a patient between 65 and 75 years of age without diabetes and no other vascular intervention than a recent infrainguinal bypass, has a 45% chance to experience a major amputation, a non-fatal myocardial infarction, a non-fatal ischaemic stroke, or to die from a vascular cause within the following 10 years. Estimating a patient's 10-year risk with the BOA Risk Chart is independent of current use of oral anticoagulants or aspirin and also of the type of bypass graft constructed, as these determinants did not contribute to our prediction

model. Without additional testing (e.g. ankle-brachial index) this chart helps the physician to quickly outline a patient's long-term prognosis and to provide accurate patient information and stimulate adequate secondary prevention treatment.

Strengths and limitations

A limitation of our study was the retrospective data collection. However, the first two years of our data collection were prospective including the recording of the baseline characteristics. Furthermore, the retrospective data collection was done in a stepwise manner to minimise the number of missed events as much as possible. Our labour intensive surveillance resulted in only four patients (1%) being completely lost to follow-up and 28 patients (6%) with a partly missing follow-up. The 32 patients with incomplete data were included in the analyses until the last recording, due to which only 224 patient-years of the potential complete observation of 3374 patient-years where lost. Therefore, with our robust data of at least 3150 patient-years we trust our risk estimations adequately reflect the true risks. Lastly, the discriminatory performances of the three consecutive prediction models were modest with the last two models having the same discriminatory value.

Figure 3. The BOA Risk Chart with the 10-year risk of the primary composite outcome event for each combination of the four independent predictors.



Legend. CLI, critical limb ischaemia

Despite a large number of outcome events, the modest discriminatory performance may in part be based on the limited number of baseline characteristics available for model development because of the pragmatic nature of the Dutch BOA Study.[10] However, in the LiLAC Study, which recorded more baseline characteristics, prognostic models for vascular events had a similarly modest discriminatory ability (AUC-ROC, 0.70 to 0.72),[15] suggesting that it is difficult to achieve good prognostication for composite vascular outcomes. A prognostic risk index for the prediction of long-term all-cause mortality instead of composite vascular outcomes in patients with an ankle-brachial index (ABI) of 0.9 or lower containing at least 10 predictors had a discriminatory performance between 0.72 and 0.80.[23] Generally, discriminatory ability of prediction models for all cause mortality may be better than that for composite vascular outcomes. This was demonstrated in the LiLAC study after TIA or non-disabling stroke, where the AUC-ROC for mortality was 0.83 and that for vascular events 0.72 in the most extended models.[15] To accurately assess the discriminatory performance of our model it is best to validate the model in an independent cohort. However, up to now no other cohort is comparable to our cohort in terms of patient characteristics, outcome events, and follow-up time to allow reliable external validation.

Conclusion

This study provided a detailed insight in the peripheral arterial disease long after infrainguinal bypass surgery and enables individual risk assessment of major fatal and non-fatal ischaemic events. Patients with PAD after infrainguinal bypass surgery are at high risk of vascular events, especially fatal vascular events. This risk remains high long after bypass surgery and demands protracted intensive secondary prevention. Our prediction model is a first step in the assessment of the patients' long-term vascular risk and helps to plan a patient specific long-term secondary prevention strategy.

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Appendix I. Definitions of outcome events.

Outcome events	Definition
Primary bypass occlusion	The first complete occlusion of the study infrainguinal bypass after surgery diagnosed by Doppler, duplex, arteriography or at open vascular surgery with or without specific clinical features.[24]
Major amputation	A lower limb amputation at the ankle or higher.
Myocardial infarction	A recorded increase of cardiospecific troponin, creatine kinase-MB, or total creatine kinase of more than twice the upper normal limit with or without a history of angina for at least 30 minutes or permanent ST segment changes, changed R-waves, or new Q waves on a standard 12-lead electrocardiography. A myocardial infarction was considered fatal if death occurred within 30 days after myocardial infarction without any other obvious cause of death present.
Ischaemic stroke	A focal neurologic deficit of sudden onset, persisting for more than 24 hours, with an increase in handicap of at least one grade on the modified Rankin scale,[25] with an ischaemic lesion on brain imaging corresponding with the clinical findings, or without an ischaemic lesion on brain imaging within two weeks after onset of symptoms excluding an intracranial haemorrhage, or without signs of a resorbing haermorrhage on brain imaging after two weeks of onset of symptoms making an intracranial haemorrhage less likely, or an intracerebral haemorrhagic infarct on brain imaging corresponding with the clinical findings. If brain imaging was not available the clinical findings were recorded as "stroke, not futher specified". Death within 30 days after stroke without any other obvious cause of death present or death beyond 30 days after stroke with an increase in handicap of at least three grades on the modified Rankin scale and without any other obvious cause of death present, were considered a fatal stroke.[26]
Minor bleeding	Requiring hospital attendance for non-fatal epistaxis, hematuria, or menorrhagia. Bleeding episodes that occurred within 30 days after a surgical intervention were excluded.
Major bleeding	Major bleeding was defined as non-fatal bleeding requiring hospital attendance, irrespective of interventions applied, including bleeding in a critical area or organ such as intracranial (confirmed by brain imaging, and different from a haemorrhagic infarction), retroperitoneal, gastro-intestinal, and intraocular bleeding, which largely corresponded with the criteria of the International Society on Thrombosis and Haemostasis (ISTH).[27] Bleeding episodes that occurred within 30 days after a surgical intervention were excluded Fatal bleeding was defined as a bleeding event that resulted in death within 30 days after bleeding and without any other obvious cause of death present.
Vascular death	Death from a vascular cause including cardiovascular causes such as myocardial infarction, congestive heart failure, arrhythmia, peripheral vascular disease, and pulmonary embolism, ischaemic stroke as cerebrovascular cause, and bleeding including haemorrhagic stroke, and other vascular causes. If death was sudden or if no clear data on the cause of death was available, the cause of death was considered to be vascular.
Non vascular death	Death from non vascular causes, including malignancy, infection, respiratory insufficiency, and non-natural death. Fatal infections with a primary focus directly related to a manifest and previously present peripheral vascular disease (e.g. infected ulcer or gangrene, aspiration pneumonia due to dysphagia after stroke) were considered a vascular death.

Chapter 4

Large variations in antithrombotic drug choice for patients after peripheral bypass surgery. Results from an international survey

Submitted

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Abstract

Introduction
An international survey among members of the European Society for Vascular Surgery (ESVS) was performed to assess vascular surgeons' preferred drug treatments and appraisal of atherosclerotic risk management in patients with peripheral arterial disease (PAD) after infrainguinal bypass surgery.

Methods
Between June 2007 and April 2008 a web-based questionnaire was accessible to vascular surgeons registered at the ESVS. Results were analysed with frequency distributions.

Results
The response rate was 34% (404/1204). The respondents had a mean practical experience of 16 years (SD +/- 10). The most prescribed antithrombotic drug after bypass surgery was aspirin (50%), followed by oral anticoagulants (22%), and the combination of aspirin and clopidogrel (14%). For venous grafts, 51% prescribed aspirin and 26% oral anticoagulants. For prosthetic grafts, 49% prescribed aspirin and 18% oral anticoagulants. Within European regions large variations in the vascular surgeons' preferred antithrombotic treatment per bypass type were seen.
Twenty-seven percent of vascular surgeons prescribed antihypertensives, mostly angiotensin converting enzyme inhibitors, and 68% lipid-lowering drugs, mostly statins.

Conclusion
Within Europe no consensus in antithrombotic treatment for patients after peripheral bypass surgery was seen. The knowledge and application of antithrombotic and additional medical treatment for secondary prevention in patients with PAD after bypass surgery is suboptimal and requires attention.

Introduction

Antithrombotic therapy effectively prevents peripheral bypass occlusion in patients with peripheral arterial disease (PAD).[1-4] Aspirin especially improves patency of non-venous conduits[5-8], whereas oral anticoagulants was found to be particularly beneficial in venous bypasses.[8,9] Antithrombotic therapy also decreases the risk of non-fatal and fatal ischaemic events in patients with PAD, who are at high risk of myocardial infarction, stroke, and vascular death.[10-13] Secondary prevention in patients with PAD by means of life-style adjustments and medical treatment with antithrombotics, antihypertensives, and statins is therefore indicated.[14-16]

Still, underdiagnosis of PAD and undertreatment of atherosclerotic risk factors in patients with PAD are reported.[17-21] One large survey performed in 1995 showed the use of antithrombotic agents after infrainguinal bypass surgery was considered routine by only 69% of 651 vascular surgeons.[21] Antithrombotic agents were prescribed rarely to never in 14% of patients, and only over a quarter received antithrombotics for less than a year after surgery.[21] In 2005, data was gathered on antithrombotic, anithypertensive, and lipid-lowering drug treatments in patients with PAD and concomitant diseases admitted for infrainguinal bypass surgery.[17] At study entry a significant percentage of patients did not receive antiplatelets (33%), beta blockers (24%), or lipid-lowering drugs (54%).[17] Most findings were based on national studies or surveys performed over 5 years ago.[17-20,22] To obtain current practice patterns throughout Europe, we performed an international survey to assess the vascular surgeon's preferred drug treatments and appraisal of cardiovascular risk management in patients with PAD after infrainguinal bypass surgery.

Methods

Participants

All vascular surgeons registered at the European Society for Vascular Surgery (ESVS) who agreed to make their contact information available to a third party, were invited to participate in our survey. Our survey was approved by the local Medical Ethics Committee. No sponsors were involved in the survey.

Data sampling

First, we inquired about the participants' demographic data, including their degree(s) in science, medical speciality, years of practical experience in vascular surgery, and their institute's academic status. Subsequently, their preferred prescription of (combined) antithrombotic treatments for patients with disabling intermittent claudication or critical limb ischaemia (CLI) after infrainguinal bypass surgery was recorded per graft material (venous or non-venous) and graft length (femoro-popliteal or femoro-crural). Additionally, prescription of anithypertensive and lipid-lowering drugs were registered. For lipid-lowering drugs, we inquired if prescription depended on serum low density lipoprotein (LDL)-cholesterol levels. Finally, the participants were

requested to grade thirteen treatment goals to minimise atherosclerotic risk according to a five-point scale from least to most important.
The questionnaire was placed on the internet at our study website and was only accessible with a password given by e-mail. Non-responders were sent electronic reminders every four weeks and a final postal reminder. Only when all obligatory items were filled out, the on-line questionnaire could be submitted successfully and the data were transferred automatically to a database.
The results were analysed with frequency distributions. For a reasonable comparison between regions, those with less than 10 participants were combined into one subgroup 'Other'.

Results

Respondents

Between June 2007 and April 2008, the online questionnaire was accessible to all 1287 enlisted ESVS-members and 839 paper questionnaires were sent to non-responders. The overall response rate was 34% (404/1204).
The respondents were primarily male (92%) with a mean age of 46 years and a mean practical experience of 16 years (Table 1). Over a third were PhD, nearly a fifth professor, and more than half of the respondents was employed in a university hospital. The respondents worked in 50 different countries geographically divided over 5 regions: North Europe, West Europe, Central Europe, South Europe, South-East Europe, and Other.

Table 1. Respondents' characteristics.

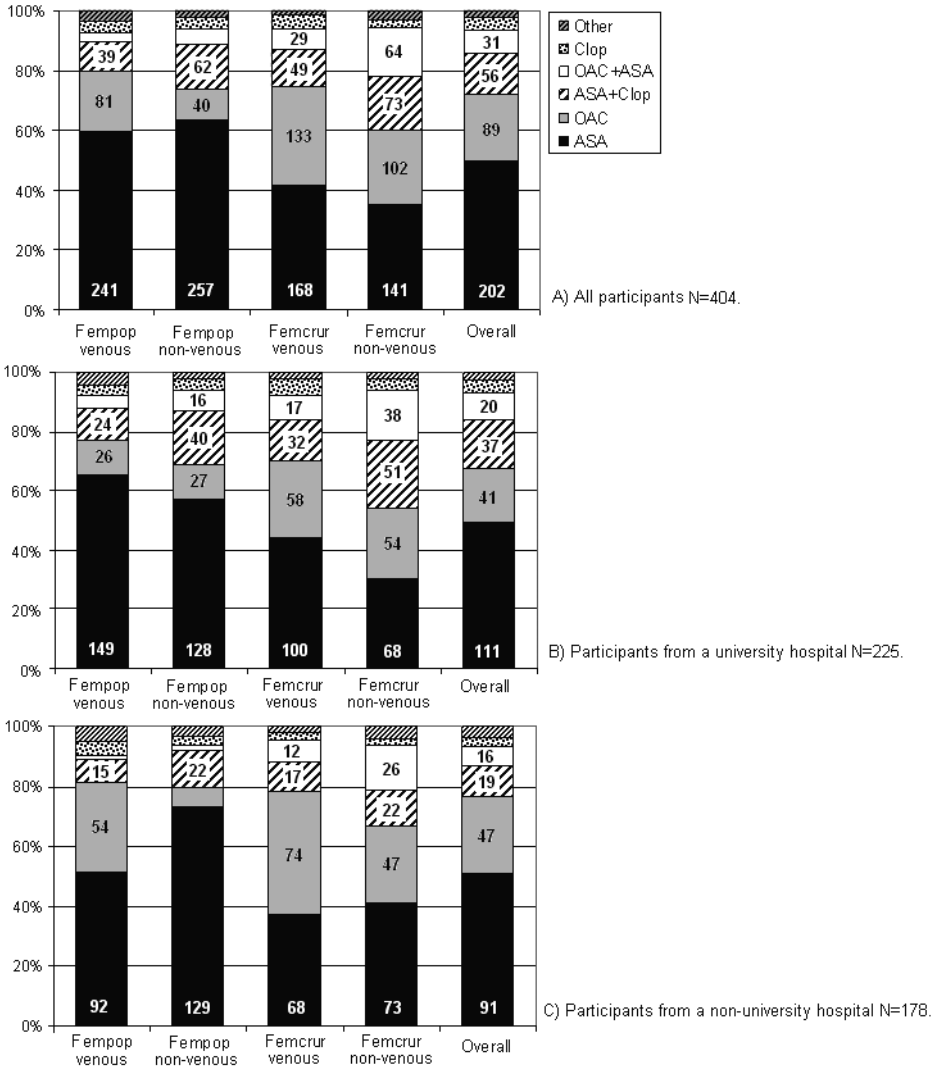
Region	Respondents N (%)	Male (%)	Mean age	Mean practical experience (years)	PhD (%)	Professor (%)	University hospital (%)
North Europe	63 (16)	90	50 (SD ± 11)	19 (SD ± 11)	50	12	64
West Europe	94 (23)	89	47 (SD ± 9)	14 (SD ± 10)	31	5	36
Central Europe	102 (25)	96	45 (SD ± 9)	17 (SD ± 10)	38	23	53
South Europe	64 (16)	88	45 (SD ± 11)	17 (SD ± 10)	37	27	73
South-East Europe	50 (12)	90	43 (SD ± 9)	14 (SD ± 9)	42	23	72
Other	31 (8)	100	46 (SD ± 9)	16 (SD ± 9)	29	3	48
Total§	404 (34)	92	46 (SD ± 10)	16 (SD ± 10)	38	18	56

Legend. SD, standard deviation. North Europe: Denmark, Estonia, Finland, Latvia, Lithuania, Norway, Sweden; West Europe: Belgium, France, Ireland, Luxemburg, Netherlands, United Kingdom; Central Europe: Austria, Czech Republic, Germany, Hungary, Poland, Slovakia, Slovenia, Switzerland; South Europe: Italy, Portugal, Spain; South East Europe: Albania, Bosnia & Herzegovina, Bulgaria, Croatia, Cyprus, Greece, Kosovo, Romania, Serbia, Turkey; Other: Argentina, Australia, Brazil, Dubai, Egypt, Georgia, India, Japan, Kuwait, New-Zealand, Philippines, Russia, Saudi-Arabia, Ukraine, United States of America, Venezuela.

Drug prescription

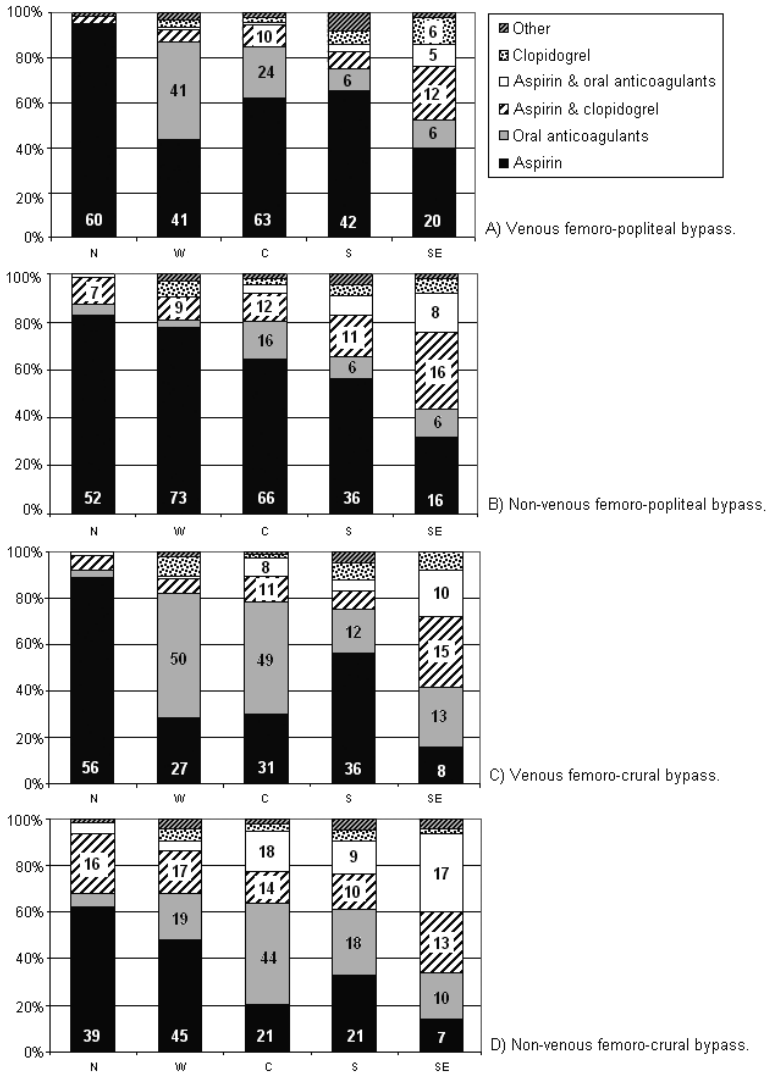
Almost all vascular surgeons prescribed antithrombotic drugs after infrainguinal bypass surgery, except for 8 (2%) participants (academic, n=1; non-academics, n=7). Among all antithrombotic drugs, aspirin was prescribed the most with 50%, followed by oral anticoagulants with 22%, and third the combination of aspirin and clopidogrel with 14% (Figure 1A). The fourth most prescribed antithrombotic treatment was aspirin with oral anticoagulants (8%). Academic participants prescribed aspirin with clopidogrel more often (17%) than non-academics (11%), while non-academics prescribed more oral anticoagulants, especially for venous grafts (Figure 1B-C). Within Europe prescription rates varied widely (Figure 2A-D).

Figure 1. Prescription of main antithrombotic agents per graft type.



Legend Figure 1. OAC, oral anticoagulants; ASA, acetylsalicylic acid; Clop, clopidogrel; Other included aspirin with dipyridamol, other antithrombotic drugs, and none; Fempop, femoro-popliteal; Femcrur, femoro-crural The prescribed antithrombotics are presented as percentages on the y-axis and as absolute numbers within the bars. In the last bar "Overall" the prescribed antithrombotics are reported as means.

Figure 2. Antithrombotic prescription rates in Europe per graft type.



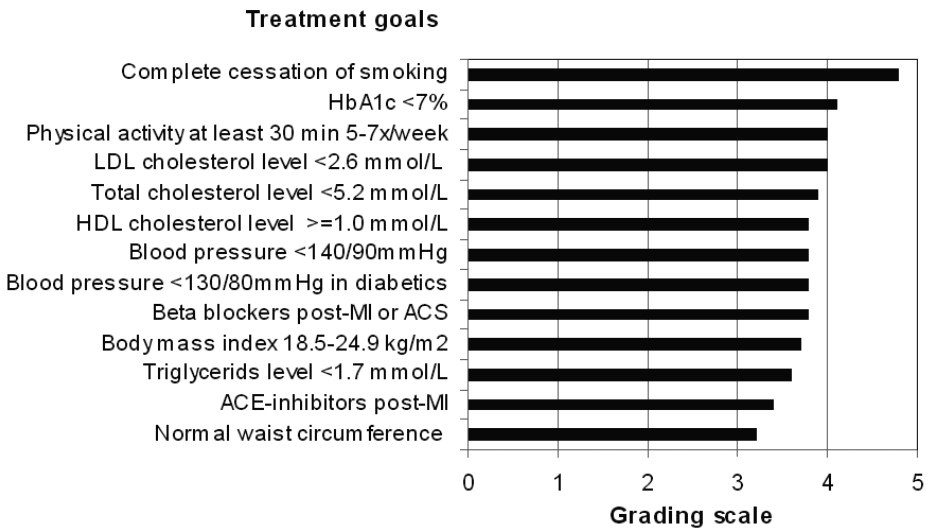
Legend. OAC, oral anticoagulants; ASA, acetylsalicylic acid; Clop, clopidogrel; Other included aspirin with dipyridamol, other antithrombotic drugs, and none; N, North; W, West; C, Central; S, South; and SE, South East Europe. The prescribed antithrombotics are presented as percentages on the y-axis and as absolute numbers within the bars.

After infrainguinal bypass surgery, anithypertensive drugs were primarily prescribed by an internist or cardiologist (67%), and far less by vascular surgeons (27%). Five % responded not to prescribe anithypertensive drugs at all. Central Europe had the highest anithypertensive drug prescription rate by vascular surgeons (31%) and Northern Europe the lowest (19%). No substantial differences were seen between academic and non-academic participants.
After surgery, lipid-lowering drugs were prescribed by an internist or cardiologist in 28% and by vascular surgeons in 68%. South Europe had most vascular surgeons prescribing lipid-lowering drugs (73%) and Central Europe least (65%). Statins were prescribed in all cases, occasionally co-administered with a fibrate (6%) or a cholesterol absorption inhibitor (6%). In 60% vascular surgeons prescribed independent of the patient's LDL-cholesterol level with percentages varying between 50% in South Europe to 76% in West Europe. No substantial differences were seen between academic and non-academic participants.

Vascular risk management

Complete cessation of smoking was found the most important treatment goal in patients after bypass surgery (Figure 3). A HbA_{1c} below 7%, physical activity for at least 30 minutes five to seven times a week, and a LDL-cholesterol level of less than 100 mg/dL (2.6 mmol/L) were appraised as very important. A normal waist circumference was considered the least important goal. No substantial differences were seen between regions or academic and non-academic participants.

Figure 3. Treatment goals to minimize atherosclerotic risk factors evaluated on a five-point scale from least (0) to most (5) important.



Legend Figure 3. HbA_{1c}, glycated hemoglobin; physical activity (at least 30 minutes 5 to7 times/week); LDL, low density lipoprotein; HDL, high density lipoprotein (males ³1.0 mmol/L; females ³1.3 mmol/L); beta-blocker use in all patients after myocardial infarction (MI) or acute coronary syndrome (ACS); ACE-inhibitors use in all patients after MI; normal waist circumference (males <102 cm; females <88 cm).

Discussion

Throughout Europe suboptimal antithrombotic and additional medical treatment in patients after peripheral bypass surgery was applied. Despite the high prescription rate of antithrombotics (98%), large variations in the vascular surgeons' preferred antithrombotic treatment per bypass type were seen with low compliance to international guideline recommendations or evidence from large clinical trials. Several level-A studies have shown antiplatelets to improve the patency of non-venous grafts more than of venous grafts,[7,8,23] and vice versa for oral anticoagulants.[8,9] We found only West Europe preferred oral anticoagulants over aspirin in venous grafts (44% for femoropopliteal bypass; 53% for femorocrural bypass). Probably, this is because international guidelines are conservative towards oral anticoagulants with its higher bleeding risk than aspirin,[1,2] and due to practical drawbacks of oral anticoagulant treatment.[8] They stress to treat only those at high risk of bypass occlusion or limb loss with oral anticoagulants.[1,2] Considering that patients with CLI and long bypasses are at the highest risk of occlusion,[24] there is a clear rationale to prescribe oral anticoagulants for at least venous femoro-crural bypasses. Still, higher prescription rates of aspirin (42%) than of oral anticoagulants (33%) were seen for venous femoro-crural bypasses.

For prevention of secondary ischaemic events, oral anticoagulants and aspirin have shown to be equally effective.[8] The combined treatment of oral anticoagulants plus aspirin was not superior to aspirin alone for prevention of major vascular events in PAD patients.[25] Instead, life-threatening, moderate, and minor bleeding episodes occurred significantly more frequent in the combined treatment group.[25] Also, the dual treatment of aspirin plus clopidogrel was as effective as aspirin alone in the prevention of major vascular events, except for myocardial infarctions.[26] More myocardial infarctions were prevented, but at the cost of an increased minor bleeding risk.[26] Guidelines recommend single treatment clopidogrel as an alternative to aspirin in patients with established atherosclerosis who do not tolerate aspirin, and discourage dual antiplatelet therapy for secondary prevention.[1-4] So, the current evidence on secondary prevention with antithrombotic therapy does not support our finding of asprin and clopidogrel being the third most prescribed antithrombotic treatment and aspirin with oral anticoagulants being the fourth most prescribed antithrombotic treatment.

The reason for the large diversity in preferred antithrombotic treatment is unclear. Despite small discrepancies due to personal preferences, one would presume the overall treatment choice to be more alike between regions when applied according to (European) guidelines and level-A evidence. Perhaps, apart from consensus on clinical

evidence, regional differences in social (e.g. patient's level of (dis)comfort and compliance), logistic (e.g. ability for INR monitoring), and economic (e.g. costs and reimbursement) aspects have more influence on drug choice than expected. A standardized multidisciplinary protocol with flow-charts for decision making on antithrombotic treatment and additional medical prevention and risk management strategies endorsed by the ESVS might stimulate European consensus.

Besides antithrombotics, blood pressure- and lipid-lowering drugs are also beneficial for secondary prevention in PAD patients.[3,4] Guidelines recommend a systolic pressure below 140 mmHg and a diastolic pressure below 90 mmHg in hypertensive PAD patients for optimal secondary prevention. In diabetics the thresholds are set below 130 and 80 mmHg, respectively.[3,4] Even independent of blood pressure control, angiotensin converting enzyme and calcium channel blockers effectively reduced cardiovascular events in PAD patients.[14,15] Most of our participants referred patients to a cardiologist or vascular internist for blood pressure control, over a quarter prescribed antihypertensive agents themselves, and 5% did neither. Perhaps a patient's routine visit to a physician assistant who maintains overview of the secondary prevention applied, can prevent inadequate care.

Most respondents prescribe lipid-lowering drugs themselves. Lifestyle modifications and statins are indicated for all PAD patients to achieve a LDL-cholesterol level below 2.6 mmol/L.[3,4,27] Aiming for target levels of each lipid fraction separately is considered more effective than controlling the total cholesterol level. [3,4,27] Nevertheless, participants evaluated the control of total cholesterol levels more important than the control of high density lipoprotein and triglyceride levels. Recent studies have found that the protective effect of statins was irrespective of LDL-cholesterol levels.[28,29] More than half of the participants seemed to have adapted their lipid control management accordingly, while more than a third had not.

To quit smoking and reach a HbA_{1c} below 7% were considered the most important treatment goals in cardiovascular risk management, as smoking and diabetes have been found the strongest PAD risk factors.[3,4,27,30] However, guidelines favour blood pressure and plasma lipid control above intensive glycemic control,[3,4,27] because in PAD patients its beneficial effects on microvascular level are not as convincing on macrovascular level.[31,32] A normal waist circumference was considered least important, while this measurement for intra-abdominal visceral fat is a stronger predictor for cardiovascular outcome than the higher evaluated body mass index (BMI).[33] Although lipid control and most treatment goals were largely applied and evaluated conform recommendations, the application and appraisal of certain risk management strategies seemed outdated as recent improvements, such as statin treatment independent of the LDL-cholesterol level, controlling lipid spectrum instead of total cholesterol and attaining a normal waist circumference instead of a normal BMI, were undervalued. An education programme on secondary prevention for vascular surgeons and a standardized ESVS-protocol have been proposed.[34] In our opinion not only the vascular

surgeon has the responsibility to keep up with new evidence on atherosclerotic risk management, but also the general practitioner. Because atherosclerosis has a high incidence and prevalence and most patients are asymptomatic,[3] the general practitioner is able to detect high risk patients earlier and prevent more adverse events than specialists who usually treat symptomatic patients at a more advanced stage of their disease. When evaluating our results, we have to consider surveys have a low level of evidence as they supply subjective measurements and selection bias is likely to occur. Half of our participants worked in an academic hospital (55.8%). This might be explained by a relatively high percentage of ESVS-members being academics and perhaps academics are more interested to participate in a survey than non-academics. Another limitation of our study is the modest response rate. Nonetheless, our results provide an indication of the current preference in several drug treatments and risk management strategies and allows for an across-border evaluation within Europe. To our knowledge, the only international survey on drug treatment after peripheral bypass surgery was conducted nearly 15 years ago and inquired after antithrombotic treatment only.[21]

Conclusion

The present survey shows pronounced differences in the preferred antithrombotic treatment within Europe and a far from optimal adherence to evidence based medicine or guidelines in the additional medical treatment of PAD patients after peripheral bypass surgery. More thorough and preferably observational studies of patients' actual drug use are needed to elucidate the extent and causes of this undertreatment in PAD patients. Nevertheless, the heterogeneity of our results imply that currently applied antithrombotic therapy after infrainguinal bypass surgery can still be improved. A rigorous change in clinical practice is needed to achieve a adequate total care of PAD patients.

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Chapter 5

Medical treatment after peripheral bypass surgery over the past decade

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Abstract

Introduction
The Dutch Bypass and Oral anticoagulants or Aspirin (BOA) Study demonstrated that in patients with peripheral arterial disease after bypass surgery oral anticoagulants were more effective in preventing venous graft occlusions than aspirin, while aspirin was more effective in non venous grafts. We evaluated if this finding was implemented in past and current clinical practice, and provided a 10-year overview of various drug treatments applied in former BOA participants.

Methods
In 482 patients from six centers that contributed most antithrombotic, antihypertensive, and lipid lowering use was recorded at baseline (n=478), retrospectively up to two years after BOA (n=388), and prospectively for patients still alive between 2005 and 2009 (n=209).

Results
At baseline, 54% of patients received antithrombotics which increased to 96% at follow-up. At baseline 15% of patients were treated with lipid lowering drugs and 49% with antihypertensives. This increased over time to 65% and 76%, respectively.

Conclusion
After the BOA Study its recommendations were applied marginally. Despite improvements over time, current lipid lowering and antihypertensive drug use remained suboptimal. Our trend analyses, however, should be interpreted with caution, because drug use and compliance in survivors might be better than average.

Introduction

Peripheral bypass surgery is a commonly accepted treatment for critical limb ischaemia (CLI), a grave condition of chronic peripheral arterial disease (PAD).[1] Unfortunately, the risk of graft failure is high.[2] Antithrombotic treatment has proven highly beneficial to prevent graft occlusion.[3] The Dutch Bypass and Oral anticoagulants or Aspirin (BOA) Study found oral anticoagulants to be more effective in preventing venous graft occlusion, while aspirin was more effective in non-venous grafts.[4] Before the Dutch BOA Study, a survey was performed among Dutch vascular surgeons to inquire after their preference in antithrombotic drug prescription for patients after infrainguinal bypass surgery.[5] After the Dutch BOA Study, the survey was repeated and showed an increased preference for aspirin for all graft types. Notably, this preference had increased the most for patients with non-venous grafts, which was supported by the results of the Dutch BOA Study.[6] However, against BOA recommendations, the preference for oral anticoagulants after venous bypass surgery had decreased. The decrease in oral anticoagulant prescription might be explained by its concomitant higher bleeding risk than aspirin and the inherent difficulties of monitoring the international normalized ratio (INR) with frequent dose adjustments. Even so, surveys only provide subjective measurements rather than actual individual drug use. To evaluate the implementation of BOA recommendations in clinical practice objectively, data on antithrombotic treatment were collected during the long-term follow-up of patients who participated in the Dutch BOA Study.

Atherosclerosis is a systemic disease. After peripheral bypass surgery patients are not only at risk of graft occlusion, but have an increased risk of myocardial infarction, stroke, or vascular death.[7] Antithrombotic treatment, blood pressure control, and low serum lipid levels reduce vascular morbidity and mortality rates in PAD patients.[8-10] Therefore, we recorded antihypertensive and lipid lowering drug use as well.

Our overall aim was to provide a 10-year overview of applied secondary medical prevention in patients with PAD before and after infrainguinal bypass surgery.

Methods

Study population

Between 1995 and 1998, the Dutch BOA Study included 2650 patients with PAD after infrainguinal bypass surgery from 77 medical centres throughout the Netherlands.[4] After surgery, patients were randomised to oral anticoagulants (phenprocoumon or acenocoumarol) with a target INR range of 3.0 to 4.5 or aspirin (100 mg carbasalate calcium once daily). Between treatment groups, the efficacy of the two antithrombotics for the prevention of infrainguinal bypass occlusion, amputation, and other vascular events was compared. Details of the Dutch BOA Study have been published elsewhere.[4] Between 2005 and 2009, a retrospective follow-up of the Dutch BOA Study was performed in 482 patients from the six centers that contributed most patients.

Data collection

The patient characteristics were registered prospectively at randomisation of the Dutch BOA Study.[4] Antithrombotic, antihypertensive, and lipid lowering drug use was recorded at study baseline, retrospectively up to two years after BOA close-out, and prospectively in patients still alive between 2005 and 2009 (Figure 1). In cases where medication was not documented at the first patient visit or at admission prior to the index admission, retrospective patient record analysis was performed. Data collection occurred in a stepwise manner. First the attending vascular surgeon was asked for the patient's drug use. Then, the general practitioner or pharmacist was contacted. When at both sources no sufficient data could be obtained, the patient was contacted. In case the patient could not be reached, the municipality office was approached to inquire if the patient had moved and to receive the patient's current home address. In case the patient had died, their relatives or acquaintances were approached for follow-up data. If none responded, the registry office was contacted to determine if the patient had died.

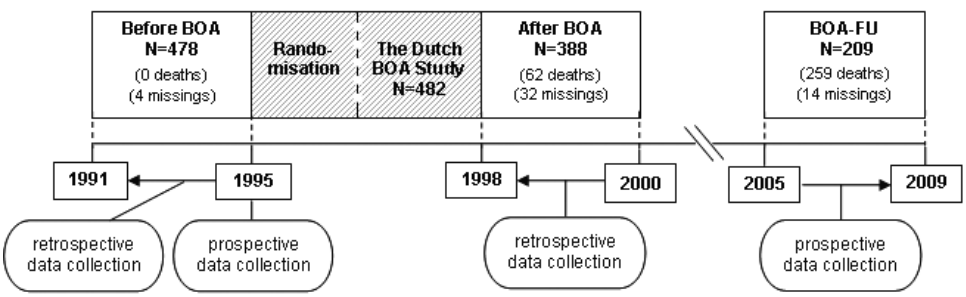
Ethical aspects

Informed consent was obtained from all patients and participants at randomisation of the Dutch BOA Study and again from patients alive at long-term follow-up. Data collection of patients who had died at time of our approach was allowed by Dutch law in the medical treatment agreement (WGBO art. 458). The authors had full access to the data, take responsibility for its integrity, and agreed to the manuscript as written.

Statistic analysis

Dichotomous data were presented as numbers and percentages, and continuous data as means with standard deviations (SD). Results were presented graphically as histograms.

Figure 1. Data collection.



Legend. Before BOA: time period up to four years before the index admission of the Dutch BOA Study in 1995; After BOA: time period up to two years after close-out of the Dutch BOA Study in 1998; BOA FU: time period from 2005 until 2009.

Results

Study population and data collection

The Dutch BOA Follow-up Study comprised 482 patients with a mean age of 69 years at randomisation (Table 1). More than half of patients were male and smoked. Other vascular risk factors, such as hypertension, diabetes mellitus, and hyperlipidaemia were present in approximately a quarter of patients. Nearly a fifth had a history of angina pectoris, myocardial infarction or stroke. About half had critical limb ischaemia (CLI) and a vascular intervention before BOA inclusion. Most procedures consisted of venous femoro-popliteal bypasses.

After retrospective completion of the data, data on drug use were available at baseline in 478 patients (4 missings; Figure 1). After the Dutch BOA Study, data on drug use were available in 388 patients (62 deaths, 32 missings). At the long-term follow-up of the Dutch BOA Study, data on drug use were available in 209 patients (259 deaths, 14 missings).

Table 1. Patient characteristics of the Dutch BOA Follow-up Study at study entry.

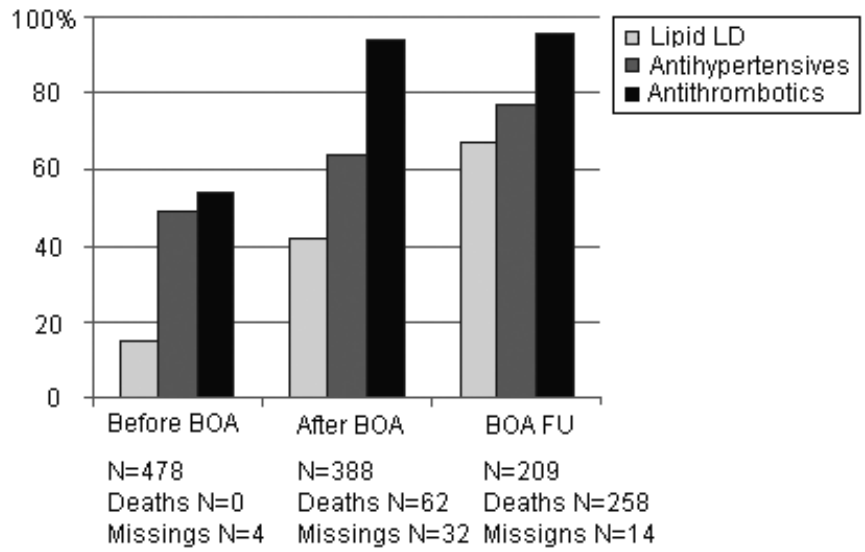
Patient characteristics	Dutch BOA Follow-up Study N=482 N (%)
Demographic facts	
Mean age at BOA randomisation	69 (SD* +/- 10)
Male gender	313 (65)
Medical history	
Smoking	289 (60)
Hypertension	186 (49)
Diabetes mellitus	109 (23)
Hyperlipaedemia	70 (15)
Angina pectoris	80 (17)
Myocardial infarction	75 (16)
Transient ischaemic attack and/or stroke	49 (10)
Vascular intervention	213 (44)
Peripheral arterial disease	
Critical limb ischaemia	220 (46)
Type of graft	
Femoro-popliteal	375 (78)
Femoro-crural	107 (22)
Vein	313 (65)
In situ	76 (16)
Reversed	230 (48)
Other	7 (2)
Biograft	38 (8)
Prosthetic	131 (27)
PTFE§	55 (11)
Dacron	62 (13)
Combined	14 (3)
Allocated trial medication (1995-1998)	
Oral anticoagulants	239 (50%)

Legend. *, standard deviation; §, polytetrafluoroethylene.

Antithrombotic drugs

The percentages of antithrombotic, antihypertensive, and lipid lowering drugs over the past decade are summarised in Figure 2. At baseline, 54% of patients received antithrombotic drugs. Overall, most patients used aspirin (37%), 15% used oral anticoagulants, and 2% used both. The retrospectively recorded antithrombotic drug use among patients with venous and non venous grafts is shown in Figure 3. Before BOA randomisation aspirin was used more than oral anticoagulants in both graft types. Up to two years after the Dutch BOA Study, in which patients were randomised between two antithrombotics, evidently the total antithrombotic drug use had increased to 94% (Figure 2). Aspirin was used in 53% of patients, 43% of patients used oral anticoagulants, and 1% used both. The use of oral anticoagulants more than doubled in both non venous and venous grafts (Figure 3).

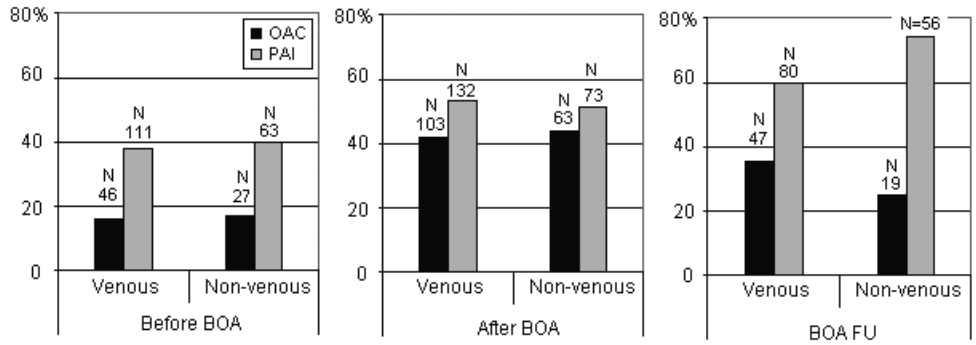
Figure 2. Percentages of drug use over time.



Legend. LD, lowering drugs; FU, follow-up; Before BOA, time period up to four years before start of the Dutch BOA Study in 1995; After BOA, time period up to two years after close-out of the Dutch BOA Study in 1998; BOA FU, time period from 2005 until 2009.

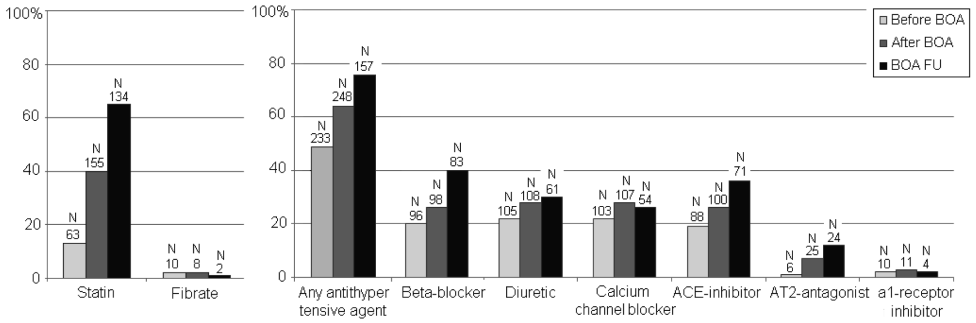
At the long-term follow-up of the Dutch BOA Study, the total antithrombotic drug use remained stable at 96% (Figure 2). The use of aspirin increased further to 65%, whereas fewer patients used oral anticoagulants (32%). The use of both antithrombotics remained 1%. In all graft types the use of aspirin increased, while the use of oral anticoagulants decreased in all graft types (Figure 3).

Figure 3. Antithrombotic drug use over time per graft material.



Legend. OAC, oral anticoagulants; PAI, platelet aggregation inhibitors; FU, follow-up; Before BOA, time period up to four years before start of the Dutch BOA Study in 1995; After BOA, time period up to two years after close-out of the Dutch BOA Study in 1998; BOA FU, time period from 2005 until 2009.

Figure 4. Lipid lowering and blood pressure lowering drug use over time.



Legend. FU, follow-up; Ca, calcium; ACE, angiotensin converting enzyme; AT2, angiotensine II receptor; selective α-1 receptor inhibitor sympathicolytic; Before BOA, time period up to four years before start of the Dutch BOA Study in 1995; After BOA, time period up to two years after close-out of the Dutch BOA Study in 1998; BOA FU, time period from 2005 until 2009.

Antihypertensive drugs

At baseline in the Dutch BOA Study 49% of patients received antihypertensive drugs (Table 1 and Figure 2). Most patients used diuretics (22%) and calcium channel blockers (22%), followed by beta-blockers (20%) and angiotensin-I converting enzym

(ACE) inhibitors (19%; Figure 4). Dual therapy was applied in 27% of patients and consisted mostly of diuretics with ACE-inhibitors (9%), followed by diuretics with calcium channel blockers (8%).
After BOA, the use of antihypertensive drugs increased to 64% (Figure 4). The preference in type of antihypertensive drug remained the same as before BOA randomisation. The use of dual therapy increased to 35%. At long-term follow-up, the use of antihypertensive drugs increased further to 76%. Currently, beta-blockers are used the most (40%), followed by ACE-inhibitors (35%), diuretics (30%), and calcium channel blockers (26%). Dual therapy is present in 45% of patients. Beta-blockers combined with ACE-inhibitors were applied the most in 15%, followed by diuretics with ACE-inhibitors in 13%.

Lipid lowering drugs
At baseline of the Dutch BOA Study, 15% of patients used lipid lowering drugs (Table 1 and Figure 2). Statins were prescribed in almost all cases (Figure 4). After the Dutch BOA Study, the use of lipid lowering drugs more than doubled to 40%. At long-term follow-up, lipid lowering drug use (statins in almost all patients) increased further to 65% (Figure 4). Dual therapy of statins with fibrates stayed below 2% before BOA, after BOA, and at long-term follow-up.

Discussion
We evaluated medical treatment over the past decade in a sample of patients from the Dutch BOA Study. Only half of patients with PAD used antithrombotics before they underwent infrainguinal bypass surgery and were enrolled in the Dutch BOA Study. It was not surprising that after the Dutch BOA Study, in which patients were randomised between oral anticoagulants and aspirin, nearly all patients (94%) still used antithrombotics. Also, at long-term follow-up the use of antithrombotic drugs remained high.
The percentages of antihypertensive and lipid lowering drug use were low before the Dutch BOA Study, especially for lipid lowering drugs, but increased over time. However, at long-term follow-up the use of antihypertensive and lipid lowering drugs remained far from optimal. Currently, only two thirds of patients or less use statins, beta-blockers, or ACE-inhibitors, despite abundant evidence that these treatments are beneficial for secondary prevention in patients with PAD.[8,9,11,12]

Antithrombotic drugs
Antithrombotic treatment of patients with PAD after infrainguinal bypass surgery has proven highly beneficial for bypass patency. Aspirin lowers the risk of bypass occlusion with about 40% in the first year after surgery (odds ratio, 0.6; 95% CI, 0.5 to 0.8).[13] Oral anticoagulants reduce the odds of bypass occlusion with 23% to 30% within one to two years after surgery.[14] Previous studies suggested, and the Dutch BOA Study con-

firmed that aspirin is especially beneficial for the patency of non venous grafts and oral anticoagulants for the patency of venous grafts.[4,15-17] However, implementation of BOA recommendations after study completion was unclear. We found that aspirin was applied the most in both graft types. Also, the use of oral anticoagulants had increased considerably in both venous and non venous grafts. For the latter conduit this was unexpected, because the Dutch BOA Study had just shown aspirin to prolong the patency of non venous grafts (hazard ratio [HR], 1.4; 95% confidence interval [CI], 1.0 to 1.6) more effectively than of venous grafts (HR, 0.7; 95% CI, 0.5 to 0.9).[4] In addition, oral anticoagulants were associated with a twofold higher bleeding risk (HR, 1.9; 95% CI, 1.4 to 2.7)[4] and generally are less favourable because of the need for monitoring the international normalized ratio (INR) and for frequent dose adjustments. Thus, there is no clear rationale to treat patients who recently received a non venous graft with oral anticoagulants. A possible explanation for this finding could be that despite the published results of the Dutch BOA Study the allocated trial medication was simply left unchanged as long as no adverse events occurred. Another explanation could be that treatment with oral anticoagulants was started in patients after occlusion of non venous grafts to improve primary assisted or secondary patency, a frequent clinical scenario.[18] However, this would probably not result in a lower risk of recurrent occlusion for reasons just mentioned, and indeed in additional analyses we found no association between occluded non venous grafts and commencing anticoagulants after the Dutch BOA Study (results not shown). At long-term follow-up the use of oral anticoagulants decreased, mostly in patients with non venous grafts, whereas the use of aspirin further increased. Still, oral anticoagulants were used in 32% of patients at long-term follow-up.

Both, aspirin and oral anticoagulants reduce the risk of myocardial infarction, stroke, and vascular death.[4,10,19] The Antithrombotic Trialists' Collaboration found antiplatelet therapy, in comparison with placebo or control, to reduce the risk of serious vascular events with 23% in PAD patients (5.8% vs. 7.1%; P<0.004).[10] Oral anticoagulants reduce mortality and cardiovascular events to a similar extent.[19,20] In the Dutch BOA Study a favourable trend was seen for oral anticoagulants versus aspirin in reducing the risk of vascular death, non-fatal myocardial infarction, non-fatal stroke or amputation (HR 0.9; 95% CI, 0.8 to 1.1), however, the trial was not powered to demonstrate a difference for this secondary composite endpoint.[4] Only a statistical significant reduced risk of ischaemic stroke was found in the oral anticoagulant group (HR, 0.5; 95% CI, 0.4 to 0.9). The risk of bleeding, including haemorrhagic strokes increased twofold with oral anticoagulants compared with aspirin (HR, 1.9; 95% CI, 1.4 to 2.7). The combined treatment of aspirin with oral anticoagulants was found to be not more efficient than aspirin alone in the prevention of ischaemic events. Both the Warfarin Antiplatelet Vascular Evaluation (WAVE) Trial and the Veterans Affairs Cooperative (VA-COOP) Trial showed no difference in the risk of the primary composite endpoint of myocardial infarction, stroke, or death from a cardiovascular cause between treatment groups.[19,20] On the backside, bleeding complications occurred two to three times more

frequent with dual antithrombotic treatment compared with aspirin alone. Therefore, most guidelines favour the use of aspirin alone over oral anticoagulants.[1,21] The eighth edition of American College of Chest Physicians (ACCP) Evidence Based Clinical Practice Guidelines recommend oral anticoagulants plus aspirin only in patients at high risk of bypass occlusion or limb loss without specifying the risk factors.[21] The PAD Antiplatelet Consensus Group and the Trans-Atlantic Inter-Society Consensus II (TASC II) both suggest to only apply oral anticoagulants in patients with a venous graft after an individual evaluation without explaining how to evaluate this.

Antihypertensive and lipid lowering drugs

Antihypertensive drugs are recommended to reduce the risk of myocardial infarction, stroke, and cardiovascular death in PAD patients with or without hypertension.[22-25] In the Heart Outcomes Prevention Evaluation (HOPE) trial the use of ramipril significantly reduced the risk of myocardial infarction (relative risk [RR], 0.8%, 95%CI 0.7 to 0.9), stroke (RR, 0.7%, 95%CI 0.6 to 0.8), and cardiovascular death (RR, 0.7%, 95%CI 0.6 to 0.9) in high risk patients.[8] Besides ACE-inhibitors, beta-blockers also decreased the risk of mortality in patients with PAD.[11] Previously, the use of beta-blockers has been discouraged in patients with PAD, because beta1-receptor blockade decreases cardiac output and induces relaxation of smooth muscle in blood vessels which was presumed to worsen claudication symptoms. However, beta-blockers do not seem to worsen PAD symptoms and are indicated in absence of contraindications such as asthma, chronic obstructive pulmonary disease, or an atrioventricular block.[22,23,26] Beta-blockers also play an important role in the perioperative setting. In patients who underwent non-cardiac vascular surgery perioperative use of beta-blockers was shown to reduce the incidence of cardiovascular death or non-fatal myocardial infarction within 30 days after surgery with a relative risk of 0.09 (95% CI, 0.02 to 0.37).[27] Alternative antihypertensive agents are calcium antagonists, diuretics, and angiotensin-II receptor antagonists, but large controlled trials that address their effect in PAD patients are lacking.[22,23] In accordance with the evidence based recommendations, beta-blockers and ACE-inhibitors were used most in our patients, but still a third of patients did not receive any antihypertensive drug for secondary prevention.
Statins are indicated for all patients with PAD whether they are symptomatic or asymptomatic and irrespective of the low density lipoprotein (LDL) cholesterol level, as statins significantly reduce the risk of cardiovascular events and death in each condition.[1,9,12,28] Still, one third of our patients was deprived of statin therapy.

Undertreatment

Previously it was recognised that patients with PAD who underwent peripheral bypass surgery often do not receive optimal secondary medical prevention. Multiple studies reported antithrombotic, antihypertensive and statin treatments, recorded between 1993 and 2006, to be below 40% to as low as 12%.[29-32] Over time little to no improvement in

the reported treatment percentages was seen; despite the fact that the clinical evidence on secondary medical prevention in PAD patients, referred to by international guidelines[1,23], piled up in the last 20 years. Already, in 1988 Kretschmer et al. reported an increased survival in patients treated with oral anticoagulants.[33] The Antiplatelet Trialists' Collaboration showed antiplatelets to reduce the risk of non-fatal and fatal ischaemic events in PAD patients in 1994.[34] Radack et al. was the first to discourage the negative effect of beta-blockers on the functional outcome in PAD patients.[26] Then, in 1999 beta-blockers were shown to significantly reduce the risk of perioperative cardiovascular events in patients who underwent non-cardiac vascular surgery.[27] The first results of ACE-inhibitors reducing the risk of non-fatal and fatal ischaemic events in PAD patients were published in the HOPE Study in 2000.[8] Duffield et al. was the first to demonstrate that plasma lipid reduction inhibited progression of atherosclerotic plaques in the femoral artery in 1983,followed by results from the Cholesterol Lowering Atherosclerosis Study (CLAS)[35] in 1991 and the Probucol Quantitative Regression Swedish Trial (PQRST)[36] in 1994. In 2002 the Heart Protection Study Group provided direct evidence that statins lowered the plasma LDL cholesterol levels, which resulted in a reduced cardiovascular risk in PAD patients.[9] With this abundant amount of high level evidence one would expect less undertreatment nowadays.

Strengths and limitations

This study provides an extensive overview on drug use in patients with PAD over more than a decade. To our knowledge, this has not been described over such a time period before. A study limitation was the partly retrospective data collection. However, the drug use at long-term follow-up for patients still alive between 2005 and 2009 was collected prospectively, including patient baseline characteristics at BOA inclusion. Another limitation was the possibility of survival bias. Patients still alive at the long-term follow-up of the Dutch BOA Study are most likely to have a relatively lower cardiovascular risk and perhaps received better secondary medical prevention compared with those deceased. Therefore, the reported percentages of drug use might even be overestimated.

Conclusion

This study was the first to describe the change in drug treatments in PAD patients over 10 years after peripheral bypass surgery. Implementation of antithrombotic therapy after peripheral bypass surgery recommended on basis of the Dutch BOA trial in the same study population was marginal, and did not seem to adhere to international guidelines either. Although, secondary medical prevention improved over time, the antihypertensive drug and statin use also remained far from optimal. There is a strong need for further improvement of applied antithrombotic and other medical therapy shortly after peripheral bypass surgery and at long-term follow-up in PAD patients. Additionally, secondary medical prevention for patients with PAD after infrainguinal bypass surgery requires optimisation as well.

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Chapter 6

The quality of life in patients after peripheral bypass surgery deteriorates at long-term follow-up

Submitted

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Abstract

Introduction
We aimed to study the long-term development of health related quality of life (HR-QoL) in patients with peripheral arterial disease after they underwent peripheral bypass surgery, and to evaluate the influence of adverse vascular events that occurred during follow-up.

Methods
We compared the current HR-QoL scores with previous measurements in patients (n=1001) who participated in the Dutch Bypass and Oral anticoagulants or Aspirin (BOA) Study. Patients from six centers that contributed most to the Dutch BOA Study were followed up retrospectively (n=482) between 1995 and 2009.

Results
At a mean follow-up of 11 years since BOA randomization, 165 of the 482 patients were alive of whom 123 (75%) completed the EQ-5D and RAND-36 questionnaires. Fifty-three patients completed the questionnaires three times: at BOA entry, at BOA close-out, and at BOA long-term follow-up. In these patients the HR-QoL scores decreased over time, especially for the physical health dimension. In comparison with the general population, matched for age, the HR-QoL scores at both BOA entry and long-term follow-up were substantially lower, even if the patient's graft was patent and no other vascular events had occurred. The occurrence of an adverse vascular event worsened the physical health state further.

Conclusion
The physical HR-QoL in patients with PAD after peripheral bypass surgery was highly impaired, independent of graft patency, and deteriorated further over time. An adverse vascular event worsened the physical health state and underlined the importance of atherosclerotic risk management as well as stimulation of physical activity in patients with peripheral arterial disease to preserve HR-QoL.

Introduction

Generally, peripheral bypass surgery is performed to improve walking distance, diminish symptoms of intermittent claudication or increase limb salvage in case of critical limb ischaemia, a grave condition of peripheral arterial disease (PAD).[1] In clinical practice, important outcome measures of bypass surgery are the technical and clinical success rates. For patients, treatment success is merely determined by their perception of change in physical, psychological, and social well-being after revascularisation. Indeed, clinically successful bypass surgery was found to significantly improve the health related quality of life (HR-QoL) in patients with critical limb ischaemia up to one year after intervention,[2] whereas symptomatic graft-related events, lower limb amputation, and ischaemic events that occurred within 21 months or less after revascularisation reduced the HR-QoL substantially.[2,3] Besides lower limb amputation, patients with PAD are also at high risk of myocardial infarction, stroke, and major bleeding.[4,5] To determine the long-term HR-QoL after peripheral bypass surgery, we assessed the present HR-QoL in PAD patients who underwent peripheral bypass surgery about 10 years ago and compared these with the HR-QoL scores obtained within two years after bypass surgery. Our second aim was to evaluate the influence of adverse vascular events that occurred after peripheral bypass surgery on the HR-QoL at long-term follow-up.

Materials and Methods

Study population

The present study population was based on the Dutch Bypass and Oral anticoagulants or Aspirin (BOA) Study.[6] Between 1995 and 1998, this multicenter randomised trial allocated 2650 patients after they underwent infrainguinal bypass surgery to treatment with oral anticoagulants or aspirin to compare the effects on preventing bypass occlusion and ischaemic complications. Full details of the Dutch BOA Study have been published elsewhere.[6] In a random sample of 1001 patients from the Dutch BOA Study the HR-QoL scores were obtained. In 746 patients from 1001 patients the HR-QoL scores were compared between patients who did and did not experience various ischaemic complications.[3]

Between 2005 and 2009 a long-term follow-up of the Dutch BOA Study was performed. A total of 482 patients from six centers that contributed the largest number of patients to the Dutch BOA Study were selected for retrospective follow-up from the last patient visit in 1998 until 2009. For the present study on HR-QoL, 165 patients alive at long-term follow-up between 2005 and 2009 were included. All patients who participated in the Dutch BOA Study and the present study gave written informed consent.

HR-QoL assessment

All 165 patients were sent the EuroQoL 5 Dimensions (EQ-5D) and the RAND-36 questionnaires by postal mail. Non-responders were sent a reminder. Incomplete questionnaires were returned to the patients for completion. If necessary, the miss-

ing questions were completed by telephone call.
The EQ-5D[7] and the RAND-36[8,9] measure the generic quality of life and are designed for self-completion by the respondent. Both are valid and reliable questionnaires[10-15], and have shown to be suitable for perceived health assessment in patients with PAD.[16-21]
The EQ-5D consists of five dimensions concerning mobility, self-care, usual activities, pain or discomfort, and anxiety or depression.[7,22] Each dimension has three levels: 1) no problems; 2) some or moderate problems; and 3) extreme problems. The combination of each selected level per dimension results in a unique EQ-5D health state, which refers to a weighted health state index that ranges from 0.0 (death) to 1.0 (perfect health). In addition, the EQ-5D includes the Visual Analogue Scale (VAS) which records the self-related health status on a vertical graduated scale from 0 (worst imaginable health state) to 100 (best imaginable health state).
The RAND-36 consists of 36 questions with standardized response choices[8,9] and which refer to eight health dimensions: physical functioning, role of limitations due to physical health problems, bodily pain, general health perceptions, vitality, social functioning, role of limitations due to emotional problems, and mental health. Each dimension is represented on a scale from 0 to 100, with a high score defining a favorable health state. The scores of the first and the last four scales are aggregated into a physical and a mental component summary score, respectively.

Collection of outcome events

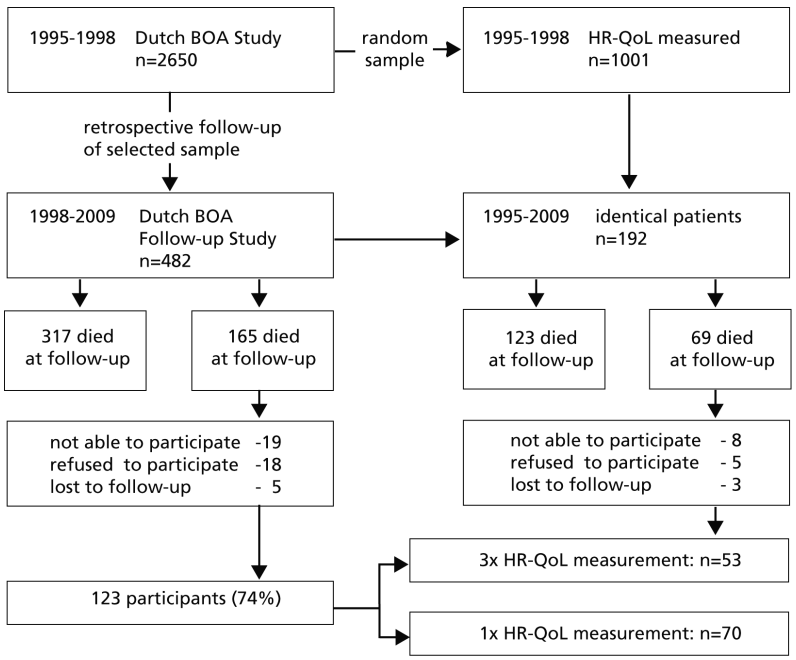
During the Dutch BOA Study follow-up visits took place at three and six months after bypass surgery and every six months thereafter. The long-term follow-up data of the selected patients were collected retrospectively from the last patient visit in April 1998 until August 2009 in a stepwise manner. The patient, the patient's attending vascular surgeon, and the patient's general practitioner were contacted to obtain information on outcome events. In case the patient had died, relatives or acquaintances were approached for follow-up data. The municipality register was asked about the last known residence if the patient had moved. If the patient, the patient's relatives or acquaintances did not respond, the registry office was contacted to inform whether the patient had died and when.
Registered and centrally adjudicated outcome events were primary bypass occlusion, non-fatal myocardial infarction, non-fatal ischaemic stroke, major amputation, minor and major bleeding, and death. The definition of each ischaemic outcome event has been published in full detail elsewhere.[6] The definition of major bleeding corresponded with the criteria of the International Society on Thrombosis and Haemostasis[23], and has also been published in full detail elsewhere.[24]

Data analysis

Descriptive statistics were used to compare patient characteristics between responders and non-responders at follow-up. Differences in characteristics with a dichotomous

outcome were reported as relative risks with corresponding 95% confidence intervals (95% CI's) and characteristics with a continuous outcome as mean differences with 95% CI's derived from an independent samples two-sided Student's t-test.
The long-term HR-QoL scores obtained at BOA follow-up were described as means with a standard deviation (SD) and compared with the short-term HR-QoL scores obtained at BOA inclusion and with the norm HR-QoL scores of the Dutch population[9,25] at the same age. Further, the long-term HR-QoL scores were compared between patients with and without adverse vascular events. Differences were reported as mean differences with corresponding 95% CI's derived from an independent samples two-sided Student's t-test.
Finally, a separate comparison was done for HR-QoL scores that were obtained thrice in the same patient; first at BOA inclusion, then at the last patient visit in BOA, and finally at long-term follow-up between 2005 and 2009. Significant changes in HR-QoL scores over time were reported as mean differences with corresponding 95% CI's derived from a paired two-sided Student's t-test.

Figure 1. Study design.



Results

Participants

Between 1995 and 1998, the Dutch BOA Study measured the HR-QoL in a total of 1001 patients over a mean follow-up of 26 months (range, 1 day to 45 months; Figure 1). Between 2005 and 2009, the long-term follow-up of the Dutch BOA Study was done in 482 patients. Of the 165 patients alive at long-term follow-up 123 patients

completed the HR-QoL-questionnaires resulting in a response rate of 75%. For the remaining 42 patients no HR-QoL data were obtained at long-term follow-up, because five were lost to follow-up, 18 refused participation, 13 patients were not able to fill out the questionnaire because it was too exhausting at their advanced age, five patients had dementia, and one patient had experienced a stroke. The 123 responders were younger than the 42 non-responders (62 and 67 years, respectively) and had fewer transient ischaemic attacks or strokes at BOA study-entry (4% and 17%, respectively; Table 1). No other statistically significant differences were seen between responders and non-responders. The mean follow-up of the 123 responders and the 42 non-responders since randomization in BOA was 11 years.

Of the 123 responders, 53 patients completed the HR-QoL-questionnaires three times (Figure 1). Their mean follow-up since randomization into BOA was 11 years.

Table 1. Characteristics of responders and non-responders at long-term follow-up.

Baseline characteristics	Responders (n=123) N (%)	Non-responders (n=42) N (%)	RR (95% CI)
Demographic factors			
Male	87 (71)	24 (57)	1.2 (0.9-1.6)
Mean age at study inclusion	62 (SD ± 9.2)	67 (SD ± 10.5)	-5.5[a] (-9.1 to -1.8)
Mean age at follow-up	73 (SD ± 9.1)	78 (SD ± 10.7)	-5.1[a] (-8.8 to -1.4)
Medical history at bypass surgery			
Angina pectoris	16 (13)	7 (17)	0.8 (0.4-1.8)
Myocardial infarction	14 (11)	6 (14)	0.8 (0.3-1.9)
TIA and/or stroke	5 (4)	7 (17)	0.2 (0.1-0.7)
ABI	0.55 (SD ± 0.23)	0.57 (SD ± 0.23)	-0.02[a] (-0.10 to 0.06)
ABI≤0.9	117 (95)	39 (93)	1.0 (0.9-1.1)
ABI≤0.6	65 (53)	24 (57)	0.9 (0.7-1.3)
Critical limb ischaemia	34 (28)	12 (29)	1.0 (0.6-1.7)
Diabetes mellitus	17 (14)	8 (19)	0.7 (0.3-1.6)
Hypertension	38 (31)	13 (31)	1.0 (0.6-1.7)
Hyperlipidaemia	39 (32)	11 (26)	1.2 (0.7-2.1)
Smoking	76 (62)	29 (69)	0.9 (0.7-1.1)
Vascular intervention	44 (36)	12 (29)	1.3 (0.7-2.1)
Trial bypass			
Femoro-crural/pedal bypass	21 (17)	8 (19)	0.9 (0.4-1.9)
Venous bypass	80 (65)	26 (62)	1.1 (0.8-1.4)
Trial medication after bypass surgery			
oral anticoagulants	62 (50)	21 (50)	1.0 (0.7-1.4)

Legend. HR-QoL, health related quality of life; RR, relative risk with 95% confidence intervals; SD, standard deviation; *a*, mean difference with corresponding 95% confidence intervals; TIA, transient ischaemic attack; ABI, ankle-brachial index.

The health related quality of life scores

In comparison with the HR-QoL scores measured shortly after BOA inclusion, the HR-QoL scores at long-term follow-up were higher for most health dimensions and

health states, reaching statistical significance for bodily pain (Table 2). Only the scores for general health and physical functioning were somewhat lower at long-term follow-up. The EQ-5D mean health state and the VAS score remained largely unchanged at long-term follow-up. In comparison with the norm scores of the Dutch population, both the short-term and long-term HR-QoL scores for all health dimensions and health states were lower, reaching statistical significance for all health dimensions and health states except for general health and the mental component summary score (Table 2).
Figure two shows the short and long-term HR-QoL scores in patients with intermittent claudication and critical limb ischaemia. The short-term HR-QoL scores in patients diagnosed with critical limb ischaemia at study entry were significantly lower for all health dimensions and health states than in patients diagnosed with intermittent claudication. Among claudicants the long-term HR-QoL scores were lower than the short-term scores. In patients with critical limb ischaemia, however, the long-term HR-QoL scores were higher than the short-term scores in all health dimensions and health states.

Table 2. HR-QoL scores at short-term and long-term follow-up.

HR-QoL	BOA Study Mean (SD) N=1001	BOA Follow-up Study Mean (SD) N=123	Mean difference (95% CI)[a]	Population norm scores N=118	Mean difference (95% CI)[b]
RAND-36					
General health	55 (23)	53 (23)	-2 (-6 to 2)	60 (24)	7 (-1 to 13)
Physical functioning	49 (28)	48 (30)	-1 (-6 to 5)	67 (26)	19 (12 to 26)
Role physical functioning	38 (43)	46 (44)	8 (0 to 16)	69 (43)	23 (12 to 34)
Bodily pain	59 (28)	67 (28)	8 (2 to 13)	75 (28)	8 (1 to 15)
Physical component summary	37 (11)	38 (12)	1 (-1 to 4)	-	-
Vitality	55 (23)	58 (24)	2 (-2 to 7)	64 (22)	6 (0.2 to 12)
Social functioning	65 (30)	70 (31)	4 (-1 to 10)	83 (24)	13 (6 to 20)
Role emotional	56 (44)	64 (44)	7 (-2 to 15)	83 (34)	19 (9 to 29)
Mental health	68 (22)	72 (22)	4 (0.2 to 8)	76 (17)	4 (-1 to 9)
Mental component summary	48 (12)	50 (13)	2 (0.2 to 4)	-	-
EQ-5D					
Mean health state	0.63 (0.30)	0.63 (0.28)	0.007 (-0.49 to 0.64)	0.88 (0.19)[c]	0.25 (0.22 to 0.28)
VAS-score	66 (20)	66 (19)	0.3 (-3.5 to 4.0)	-	-

Legend. HR-QoL, health related quality of life; SD, deviation; 95% CI, 95% confidence interval; a, comparison of the HR-QoL scores at BOA inclusion with the scores at BOA long term follow-up; *b*, comparison of the HR-QoL scores at BOA long term follow-up with the norm scores of the Dutch population; VAS, visual analogue scale; *c*, based on a cohort of n=9685.

Figure 2. HR-QoL scores at BOA inclusion and at long-term follow-up for patients diagnosed with intermittent claudication or critical limb ischaemia at study entry.

Legend. At BOA inclusion the scores for all health dimensions and health states were statistically significantly lower in patients with critical limb ischaemia compared with the scores in patients with intermittent claudication (numbers not reported). HR-QoL, health related quality of life; 95% CI, 95% confidence interval; *(**), statistical significance; PCS, physical component summary; MCS, mental component summary; EQ-5D, Euro-QoL 5D mean health state; VAS, visual analogue scale.

Table 3. Number of experienced vascular events at long-term follow-up.

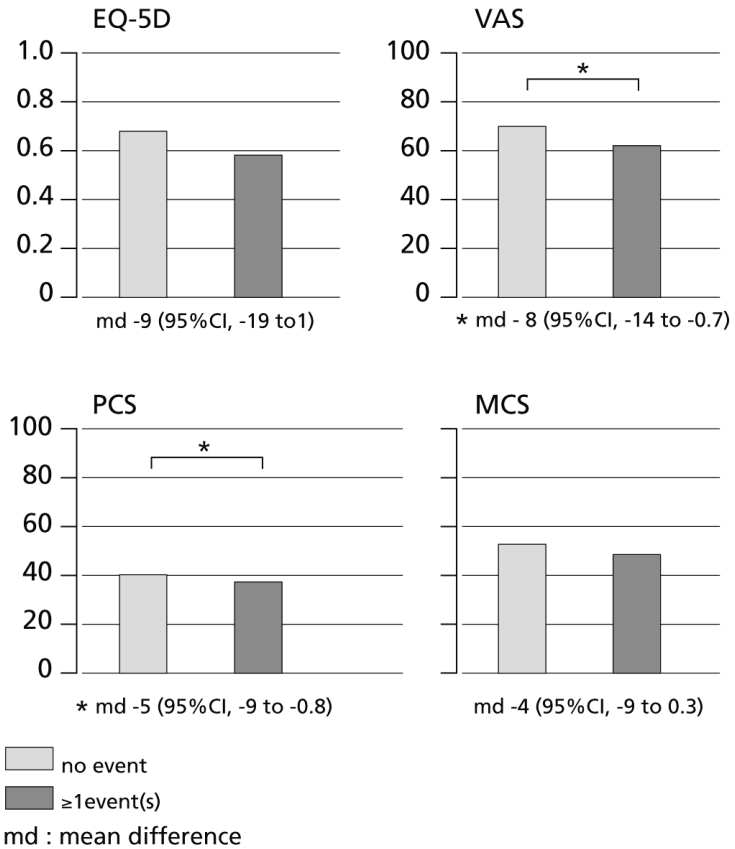
Vascular events	Responders N=123 (%)
No event	61 (50)
1 event:	42 (34)
-primary bypass occlusion	28 (67)
-major amputations	1 (2)
-myocardial infarction	6 (14)
-ischaemic stroke	5 (12)
-major bleeding	2 (5)
2 events	14 (11)
≥ 3 events	6 (5)

At long-term follow-up, half of the responders had experienced at least one adverse vascular event (i.e. ischaemic or bleeding; Table 3). The mean HR-QoL scores after the occurrence of an adverse vascular event were lower for all health dimensions and health states compared with the scores of responders who did not experience an adverse vascular event, reaching statistical significance for the VAS score and the physical component summary score (Figure 3). In patients after primary bypass occlusion (n=28) a statistically significant lower score for physical functioning (44 vs. 58; mean difference, 14; 95% CI, 1 to 27), physical role (35 vs 57; mean difference, 22; 95% CI, 3 to 42), and emotional role (50 vs. 77; mean difference, 27; 95 %CI, 7 to 47) were seen in comparison with the scores in patients with a patent graft (n=61). The scores for pain (59 vs. 68; mean difference, 9; 95% CI, -4 to 22) and social functioning (68 vs. 75; mean difference, 7; 95% CI, -6 to 20) were also lower, but without reaching statistical significance. The HR-QoL scores in patients who experienced one or two adverse vascular events other than graft failure (n=17) were slightly lower than the scores in patients who experienced graft failure only (n=28), without reaching statistical significance. Patients with a patent graft and no other adverse vascular events (n=61) scored lower than the general Dutch population for all health dimensions and health states, reaching statistical significance for physical functioning (58 vs. 67; mean difference, 9; 95% CI, 1 to 18), physical role (57 vs. 69; mean difference, 12; 95% CI, 2 to 22), bodily pain (68 vs. 75; mean difference, 7; 95% CI, 1 to 13), social functioning (75 vs. 83; mean difference, 8; 95% CI, 2 to 14), and the mean health state (0.68 vs. 0.88; mean difference, 0.20; 95% CI, 0.14 to 0.26). Our study did not contain enough patients with a major lower limb amputation (n=11) to allow for reliable comparisons of HR-QoL scores in patients without a major amputation.

Fifty-three responders completed the HR-QoL questionnaires three times during follow-up (Figure 4). Over time a decrease was seen for all mean HR-QoL scores, except for bodily pain, mental health, and the mental component summary score, which remained largely unchanged over time. The physical functioning score and the

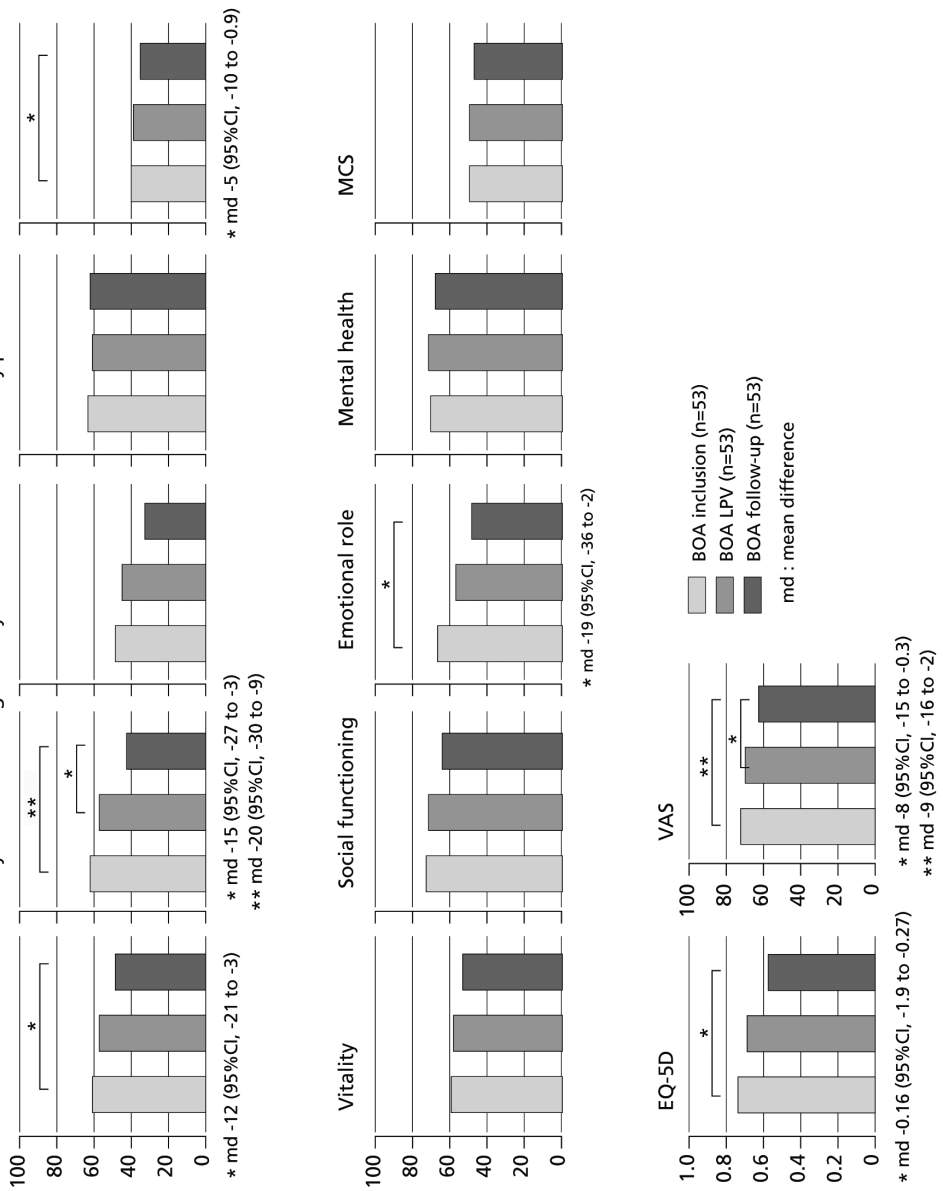
VAS score decreased significantly between the last patient visit for BOA and at BOA long-term follow-up (Figure 4). Between BOA inclusion and BOA long-term follow-up, the scores for general health, physical functioning, physical component summary, emotional role, EQ-5D mean health state, and VAS decreased significantly (Figure 4).

Figure 3. HR-QoL scores per number of adverse vascular events.



Legend. HR-QoL, health related quality of life; 95% CI, 95% confidence interval; EQ-5D, Euro-QoL 5D mean health state; VAS, visual analogue scale; *, statistical significance; PCS, physical component summary; MCS, mental component summary.

Figure 4. HR-QoL scores at BOA inclusion, close-out, and long-term follow-up for 53 patients.



Legend. HR-QoL, health related quality of life; LPV, last patient visit; 95% CI, 95% confidence interval; *(*), statistical significance; PCS, physical component summary; MCS, mental component summary; EQ-5D, Euro-QoL 5D mean health state; VAS, visual analogue scale.

Discussion

We have studied the change in HR-QoL over a mean period of 11 years in patients with PAD after peripheral bypass surgery. In comparison with the general population, patients with PAD have a considerably lower physical HR-QoL, even if they have a patent graft and experienced no other adverse vascular events. Over time the physical HR-QoL in PAD patients deteriorated further, while mental health and the perception of pain remained fairly stable. The occurrence of an adverse vascular event lowered the physical HR-QoL even more.

Our findings are in agreement with other studies. The Peripheral Arterial Disease Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) Program found the physical component summary score to be significantly lower in patients with PAD than in patients without PAD.[26] The mental component summary score, however, did not differ between patients with or without PAD.[26] Corresponding results were found in the Edinburgh Artery Study, but only for patients with symptomatic PAD.[27] In patients with asymptomatic PAD the HR-QoL did not differ from patients without PAD.[27] Moreover, the HR-QoL was found to decrease significantly with an increasing severity of symptomatic PAD.[17,18,21] The largest decrements were seen for physical functioning, social functioning, pain, and physical role.[17] The scores for mental health decreased only marginally despite PAD worsening from mild claudication to tissue loss.[17] In our study the HR-QoL scores meausured shortly after BOA inclusion were substantially lower in patients with critical limb ischaemia than in claudicants. However, at long-term follow-up the HR-QoL scores improved, especially in patients who were diagnosed with critical limb ischaemia at BOA study-entry. This may partly be explained by survival bias, as long-term survivors probably have a better health state and HR-QoL compared with those who deceased. Moreover, the 123 responders probably had a better health state than the 42 non-responders at long-term follow-up. Nevertheless, this finding supports the long-term benefit in terms of HR-QoL that can be obtained with bypass surgery in patients with critical limb ischaemia.

To our knowledge, only one other study described the changes in HR-QoL in PAD patients after revascularisation at long-term follow-up.[28] The HR-QoL scores significantly improved shortly after successful revascularisation, as shown before in other studies[29,30], and remained largely unchanged up to one year after revascularisation. However, at four years after revascularisation physical mobility deteriorated, reaching statistical significance in patients with critical limb ischaemia.[28] Only the scores for pain remained improved up to four years after revascularisation.[28] These observed changes in HR-QoL after revascularisation corresponded well with our findings in 53 patients with three consecutive measurements over a mean period of 11 years. Also the scores in 123 patients alive at long-term follow-up seemed to show the same trend with higher scores for bodily pain and lower scores for general health and physical functioning long after revascularisation compared with scores measured shortly after

peripheral bypass surgery, These results, however, are based on a single measurement and are probably higher than average due to survival bias, as mentioned earlier. The consecutive measurements in 53 patients are therefore considered more reliable and illustrative for the change of the HR-QoL at 11 years after peripheral bypass surgery. No clear explanation could be found for the fairly stable scores found for bodily pain and mental health, whereas the scores for the other dimensions and health states decreased over time. We assumed that perhaps coping mechanisms made the perception of pain become less pronounced over time and enables to adapt the mental health state to new conditions.

Not only does the HR-QoL deteriorate over time, but the HR-QoL also worsens substantially after the occurrence of an adverse vascular event. After a bypass occlusion a patient's physical health was lower than in patients with a patent graft, and decreased even more in patients who experienced an adverse vascular event other than bypass occlusion. Unfortunately, we were not able to distinguish the HR-QoL scores between the types of events due to too few numbers of the respective events. The patients who participated in our study were derived from the Dutch BOA Study.[6] In the Dutch BOA Study the largest differences in health dimensions were seen after graft failure and lower limb amputation in comparison with patients without an ischaemic event.[3] A symptomatic bypass occlusion or a second revascularisation significantly lowered a patient's pain score and social functioning score. After a lower limb amputation the lowest scores were reached in almost all health dimensions, especially in physical functioning, physical role, and emotional role. This finding is in line with a study that compared the HR-QoL in 130 amputees with the HR-QoL in 115 controls.[31] The amputees had significantly worse scores for all health dimensions, especially for physical health.[31] According to these results limb salvage is important to prevent worsening of a patient's HR-QoL. Peripheral bypass surgery is able to relieve lower limb complaints and avoid amputation on the short term, but did not prove to be durable for limb salvage and HR-QoL scores. To stabilize the HR-QoL in patients with PAD as long as possible atherosclerotic risk management through lifestyle modifications and drug treatments might be just as important as surgical intervention.

A possible limitation of our study is the relatively small number of patients with consecutive measurements of HR-QoL. However, this is inevitable in long-term follow-up studies of patients at high risk of vascular morbidity and mortality. Our study is the first to describe the change in the HR-QoL in patients with PAD over a mean period of 11 years after infrainguinal bypass surgery. Further prospective long-term studies in even larger populations are needed to gain insight in HR-QoL, taking the various disease states and complications that occur because of atherosclerosis into account.

Conclusion

Patients with PAD after peripheral bypass surgery have a substantially impaired HR-QoL even if their graft is patent. Over time their HR-QoL deteriorates further, mainly driven by a reduced physical health. A patient's physical health worsens further after the occurrence of an adverse vascular event. This underlines the importance of secondary prevention and optimal health care in PAD patients to preserve the QoL.

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Chapter 7

Bleeding increases the risk of ischaemic events in patients with peripheral arterial disease.

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Abstract

Introduction
Patients with peripheral arterial disease are at high risk of ischaemic events and therefore are treated with antithrombotics. In patients with coronary artery disease or cerebrovascular disease, bleeding is related to the subsequent occurrence of ischaemic events. Our objective was to assess whether this is also the case in patients with peripheral arterial disease.

Methods and Results
All patients from the Dutch Bypass and Oral Anticoagulants or Aspirin (BOA) Study, a multicenter randomised trial comparing oral anticoagulants with aspirin after infrainguinal bypass surgery, were included. The primary outcome event was the composite of non-fatal myocardial infarction, non-fatal ischaemic stroke, major amputation, and cardiovascular death. To identify major bleeding as an independent predictor for ischaemic events, crude and adjusted hazard ratio's with 95% confidence intervals were calculated with multivariable Cox regression models.
From 1995 until 1998, 2650 patients were included with 101 nonfatal major bleedings. During a mean follow-up of 14 months, the primary outcome event occurred in 218 patients; 22 events were preceded by a major bleeding. The mean time between major bleeding and the primary outcome event was 4 months. Major bleeding was associated with a 3-fold increased risk of subsequent ischaemic events (crude hazard ratio, 3.0; 95% confidence interval, 1.9 to 4.6; adjusted hazard ratio, 3.0; 95% confidence interval, 1.9 to 4.7).

Conclusion
In patients with peripheral arterial disease, as in patients with coronary artery disease or cerebrovascular disease, major bleeding was independently associated with major ischaemic complications. Without compromising the benefits of antithrombotics, these findings call for caution relative to the risks of major bleeding.

Introduction

Peripheral arterial disease (PAD) resulting from atherosclerosis is a major public health burden, with a prevalence of ~27 million people in Europe and North America.[1] Because atherosclerosis is a progressive and systemic disease, patients with PAD are at a high risk of cardiovascular and cerebrovascular ischaemic events, including fatal events.[2] The risk of death from a cardiovascular cause in 10 years is 3 to 6 times greater in patients with PAD compared with patients without PAD.[3] Thus, patients with PAD should be treated with antithrombotics to prevent these ischaemic events.[4,5]

The main adverse effect of antithrombotic therapy is the risk of bleeding.[6] Non-fatal bleeding leads not only to great discomfort at the time of bleeding but also to more harmful and even life-threatening ischaemic events in the long term. In patients with coronary artery disease (CAD), bleeding was found to be independently associated with the occurrence of ischaemic events within 30 days to 1 year after bleeding.[7-11] Recent studies in patients admitted with an acute coronary syndrome have shown that bleeding led to a 4- to 10-fold increased risk of death, myocardial infarction, or stroke during hospital admission with a graded response related to the severity of bleeding.[7-10] In addition, patients who were admitted with an acute ischaemic stroke had a 3- to 4-fold increased risk of in-hospital recurrent stroke, myocardial infarction, and death or severe dependence at discharge.[12]

To the best of our knowledge, the ischaemic consequences of bleeding, possibly promoted by antithrombotic treatment, have been described only in patients with CAD or cerebrovascular disease and have not yet been studied in patients with PAD. Patients with PAD have a vascular morbidity and mortality at least as high as patients with CAD or cerebrovascular disease.[2] Additionally, patients with PAD show a trend towards a higher incidence of bleeding.[2,13] Hence, our aim was to study the influence of major bleeding on the risk of subsequent ischaemic events in patients with PAD receiving antithrombotic therapy in a large randomised controlled trial.

Methods

Patients and treatment

All patients in the Dutch Bypass and Oral Anticoagulants or Aspirin (BOA) Study were included in the present study. Full details of the Dutch BOA Study have been published elsewhere,[14] and are briefly summarised here. Between 1995 and 1998, this multicenter randomised trial included a total of 2650 patients with PAD after infrainguinal bypass surgery. The effectiveness of oral anticoagulation with phenprocoumon or acenocoumarol with a target international normalized ratio range of 3.0 to 4.5 was compared with that of aspirin (100 mg carbasalate calcium daily) for the prevention of infrainguinal bypass occlusion, amputation, and other vascular events. Follow-up visits took place at 3 and 6 months after surgery and every 6 months thereafter to record graft patency, the occurrence of ischaemic or bleeding complications, and adherence to trial medication.

Outcome events

Major bleeding was defined as non-fatal bleeding requiring hospital attendance regardless of the interventions applied, including bleeding in a critical area or organ, ie, intracranial, retroperitoneal, gastrointestinal, and intraocular bleeding, which largely corresponded with the criteria of the International Society on Thrombosis and Haemostasis .[15] Hospital attendance for epistaxis, haematuria and menorrhagia was defined as minor bleedings. Bleeding episodes that occurred within 30 days after surgery were excluded from the present study because they were considered surgery related.

The primary outcome event was the composite of death resulting from cardiovascular causes, non-fatal myocardial infarction, non-fatal ischaemic stroke, or major amputation above the ankle (whichever occurred first during follow-up). Secondary outcome events were death resulting from all causes, death resulting from cardiovascular causes, fatal or non-fatal myocardial infarction, fatal or non-fatal ischaemic stroke, major amputation, and the composite of death resulting from cardiovascular causes, non-fatal myocardial infarction, and non-fatal ischaemic stroke. Death resulting from cardiovascular causes did not include fatal bleedings; however, a sensitivity analysis was done in which we included fatal bleedings. Fatal bleeding was defined as a bleeding event that resulted in death within 30 days after bleeding. In addition, sensitivity analyses were conducted with intracranial and intraocular bleedings excluded.

Statistical Analyses

Baseline variables with a continuous outcome were summarised as means and discrete variables as frequencies and percentages. Any missing data were imputed with single linear regression analysis incorporating variables associated with the missing data. In patients with multiple bleedings, the bleeding that occurred first was the index bleeding. Baseline characteristics associated with major bleeding were estimated with univariable Cox regression models and reported as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). Those with a value of $P \leq 0.25$ were introduced in a multivariable Cox regression model to identify independent predictors for major bleeding. All models incorporated major bleeding as dependent variable and baseline characteristics as independent variables with time from study entry to index bleeding or last follow-up. In analyses of the association between bleeding and vascular events, the time of major bleeding was considered the start date. To equalize the start date between bleeders and non-bleeders, the start date of non-bleeders was pushed up with the mean time between study entry and the index bleeding. Patients without any follow-up time left after the mean time to indexbleeding was subtracted from their total follow-up time were excluded from further analyses.

Only outcome events that occurred after the start date were included. Non-fatal ischaemic events that occurred before index bleeding or within the censored follow-up time were considered medical history and added to the baseline variables for further analyses. Risks of vascular events in patients with and without bleeding were compared with HRs

and corresponding 95% CIs. Crude HRs were derived from univariable Cox regression models, with the primary outcome event incorporated as the dependent variable and bleeding as the independent variable with time from start date to the first outcome event or last follow-up. Adjusted HRs were calculated by including independent predictors for bleeding in the multivariable Cox regression model. Additional analyses were done for the first 30 days of follow-up and from that time up to 40 months. The assumption of proportionality of the hazards for events over time was tested with the Schoenfeld test. To assess whether HRs differed between patients treated with aspirin and those treated with oral anticoagulation, we calculated the interaction term of bleeding and trial medication. The occurrence of the primary outcome event for patients with and without major bleeding is presented graphically as Kaplan-Meier curves stratified for trial medication. Separate analyses were done for minor bleedings.
The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patients and follow-up

A total of 2650 patients were included in our study. The baseline characteristics of the patients (64% male; mean age, 69 years; median age, 70 years) are listed in Table 1.

Table 1. Baseline characteristics among patients with and without a major bleeding; differences are expressed as hazard ratio's with 95% confidence intervals (95% CI) with time from study entry to first major bleeding or last follow-up.

Baseline characteristics	Major bleeding present (n=101) N (%)	Major bleeding absent (n=2549) N (%)	Hazard ratio (95% CI)
Demographic characteristics			
Male	61 (60)	1637 (64)	0.9 (0.6-1.3)
Median age >70 years	62 (61)	1264 (50)	1.7 (1.1-2.5)
Age, mean ±SD*, years	72 ± 9.5	6 9± 10.0	1.041 (1.019-1.064)†
Medical History			
Angina pectoris	22 (22)	414 (16)	1.4 (0.9-2.3)
Myocardial infarction	22 (22)	442 (17)	1.4 (0.9-2.2)
TIA‡ and/or stroke	16 (16)	290 (11)	1.6 (0.9-2.7)
ABI§ ≤0.9	95 (94)	2396 (94)	1.0 (0.5-2.3)
ABI ≤0.6	71 (70)	1689 (66)	1.2 (0.8-1.9)
Critical limb ischaemia	65 (64)	1230 (48)	2.0 (1.3-3.0)
Diabetes Mellitus	34 (34)	666 (26)	1.5 (1.0-2.2)
Hypertension	48 (48)	983 (39)	1.4 (1.0-2.1)
Hyperlipidaemia	18 (18)	418 (16)	1.1 (0.7-1.9)
Smoking	48 (48)	1390 (55)	0.7 (0.5-1.1)
Vascular intervention	48 (48)	1154 (45)	1.1 (0.7-1.6)
Trial Bypass			
Femoro-crural/pedal bypass	28 (28)	503 (20)	1.6 (1.0-2.5)
Venous bypass	60 (59)	1486 (58)	1.0 (0.7-1. 5)
Trial Medication			
Oral anticoagulants	72 (71)	1254 (49)	2.5 (1.6-3.9)

Legend Table 1. *, standard deviation; †, hazard ratio based on age as a continuous variable; ‡, transient ischaemic attack; §, ankle-brachial index.

The mean time between randomisation and major bleeding was 9.2 months (range, 0 to 37.5 months). Patients without major bleeding and a total follow-up of ≤9.2 months (n=420) were excluded from further analyses. The remaining 2230 patients had a mean follow-up of 14 months (range, 0 to 39 months). When minor bleedings were included, the mean time between randomisation and occurrence of major or minor bleeding was 9.9 months (range, 0 to 37.5 months). Patients without any bleeding and a total follow-up of ≤9.9 months (n=464) were excluded from further analyses. The remaining 2186 patients had a mean follow-up of 14 months (range, 0 to 39 months).

Incidence and Predictors of Bleeding

A total of 120 initial major bleeding events (4.5%) occurred, 19 of which were fatal (Table 2). Nine of the initial major bleeding events were followed by a second fatal bleeding, resulting in a total of 28 fatal bleedings. Of the 101 initial non-fatal major bleedings, almost half were gastro-intestinal bleedings (48%), followed by intracranial bleedings (9%). Blood transfusions were given in 20 patients, and 20 patients stopped their allocated trial medication after index bleeding.

Table 2. Bleeding characteristics per trial medication.

Bleeding characteristics	Aspirin N (%)	Oral anticoagulants N (%)
Non-fatal major bleeding	29	72
- Gastro intestinal	23 (79)	44 (61)
- Intracranial	1 (3)	8 (11)
- Intraocular	0 (0)	7 (10)
- Haemoptysis	2 (7)	2 (3)
- Other	3 (10)	11 (15)
Non-fatal minor bleeding	19	26
- Haematuria	15 (79)	16 (62)
- Epistaxis	4 (21)	8 (31)
- Menorrhagia	0 (0)	2 (8)
Fatal Bleeding	11	17
Blood Transfusion	6	14

Patients who experienced a major bleeding were older; had critical limb ischaemia with ulcers or gangrene, diabetes mellitus, and hypertension; and were more frequently allocated to oral anticoagulants compared with patients without major bleeding (Table 1). Patients without major bleeding more often had intermittent claudication without signs of critical limb ischaemia and more frequently received a femoropopliteal bypass with the distal anastomosis above the knee compared with patients who did experience a major bleeding. Independent predictors for major bleeding were age

(HR, 1.032 per year; 95% CI, 1.010 to 1.055), use of oral anticoagulants (HR, 2.5; 95% CI, 1.6 to 3.8), and critical limb ischaemia (HR, 1.7; 95% CI, 1.1 to 2.5).
In total 45 initial minor bleedings occurred. The majority of these minor bleedings were haematuria (69%), followed by epistaxis (27%) and menorrhagia (4%; Table 2).

Outcome Events

The primary outcome event occurred in 218 patients: 98 (45%) in the anticoagulant group and 120 (55%) in the aspirin group (Table 3). A first myocardial infarction occurred in 36 patients, a first ischaemic stroke in 37 patients, a first major amputation in 67 patients, cardiovascular death in 127 patients, and all-cause death in 240 patients.

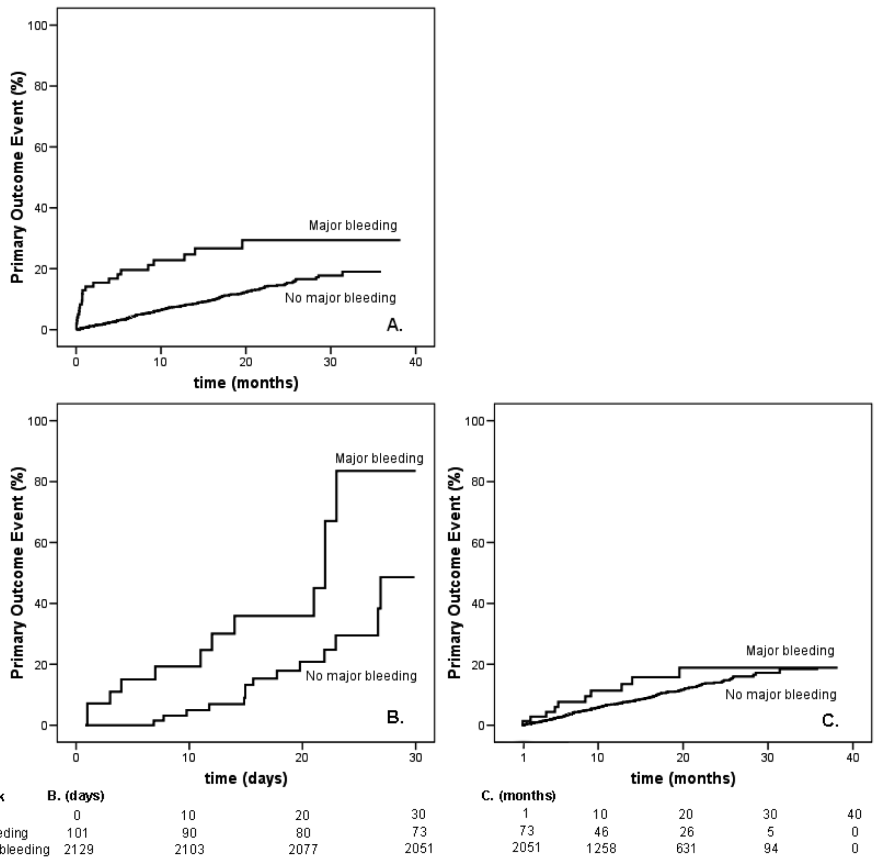
Table 3. Primary and secondary outcome events among patients with and without major bleeding; differences are expressed as crude and adjusted hazard ratio's (HR) with 95% confidence intervals (95% CI) with time from first major bleeding to first outcome event or last follow-up.

Outcome events	Major bleeding present (n=101) N (%)	Major bleeding absent (n=2129) N (%)	Crude HR (95% CI)	Adjusted HR* (95% CI)
Primary outcome	22 (22)	196 (9)	3.0 (1.9-4.6)	3.0 (1.9-4.7)
Secondary outcomes:				
-myocardial infarction (MI)	3 (3)	33 (2)	2.3 (0.7-7.6)	2.4 (0.7-8.0)
-ischaemic stroke (IS)	4 (4)	33 (2)	3.1 (1.1-8.8)	4.0 (1.4-11.6)
-major amputations	4 (4)	63 (3)	1.8 (0.6-4.8)	1.8 (0.7-5.1)
-cardiovascular death	18 (18)	109 (5)	4.2 (2.6-7.0)	3.8 (2.3-6.3)
-all-cause death	38 (38)	202 (10)	4.8 (3.4-6.8)	4.3 (3.1-6.2)
-composite of non-fatal MI, non-fatal IS, and cardiovascular death	20 (20)	144 (7)	3.5 (2.2-5.6)	3.2 (2.0-5.1)
- Oral anticoagulants (n=1120)	72 (71)	1048 (49)		
Primary outcome	15 (21)	83 (8)	3.1 (1.8-5.3)	2.9 (1.6-5.0)
Secondary outcomes:				
-myocardial infarction	1 (1)	15 (1)	NE	NE
-ischaemic stroke	2 (3)	7 (1)	4.7 (1.0-22.5)	4.7 (1.0-22.5)
-major amputations	3 (4)	25 (2)	2.1 (0.6-7.1)	1.9 (0.6-6.5)
-cardiovascular death	14 (19)	49 (5)	4.8 (2.6-8.6)	4.2 (2.3-7.6)
-all-cause death	26 (36)	101 (10)	4.3 (2.8-6.6)	3.8 (2.5-5.9)
-composite of non-fatal MI, non-fatal IS, and cardiovascular death	14 (19)	62 (6)	3.7 (2.1-6.6)	3.3 (1.9-6.0)
- Aspirin (n=1110)	29 (29)	1081 (51)		
Primary outcome	7 (24)	113 (11)	3.7 (1.7-8.0)	3.4 (1.6-7.4)
Secondary outcomes:				
-myocardial infarction	2 (7)	18 (2)	6.3 (1.5-27.2)	6.3 (1.5-17.2)
-ischaemic stroke	2 (7)	26 (3)	4.3 (1.0 -18.3)	4.0 (1.4-11.7)
-major amputations	1 (3)	38 (4)	1.6 (0.2-11.6)	1.5 (0.2-11.2)
-cardiovascular death	4 (14)	60 (6)	3.6 (1.3-10.0)	3.7 (1.4-10.3)
-all-cause death	12 (41)	101 (9)	6.3 (3.5-11.6)	6.1 (3.3-11.1)
-composite of non-fatal MI, non-fatal IS, and cardiovascular death	6 (21)	82 (8)	4.0 (1.7-9.1)	3.9 (1.7-9.0)

Legend Table 3. *, hazard ratio adjusted for the independent predictors of major bleeding in a multivariable Cox regression model; NE, not estimable.

The mean time between major bleeding and the primary outcome event was 3.9 months (range, 0 to19.6 months). Of the 101 patients with a non-fatal major bleeding, 22 patients (22%) had a primary outcome event compared with 196 events (9%) in 2230 patients without a major bleeding (crude HR, 3.0; 95% CI, 1.9 to 4.6; Table 3 and Figure 1A). After multivariable adjustment, the risk of the primary outcome event remained 3 times higher in patients with a previous major bleeding compared with those without major bleeding (adjusted HR, 3.0; 95% CI, 1.9 to 4.7). Although no violation of proportional hazards was found for the first 30 days after the start date (P= 0.375) and from 1 to 40 months of follow-up (P= 0.162), the increased risk of the primary outcome event was present mainly in the first 30 days after bleeding (adjusted HR, 3.3; 95% CI, 1.5 to 7.2; Figure 1B) compared with the risk from 1 to 40 months after bleeding (adjusted HR, 1.5; 95% CI, 0.8 to 2.9; Figure 1C).

Figure 1. Kaplan-Meier estimates of cumulative percentages of the primary outcome in patients who experienced a major bleeding and those who did not.

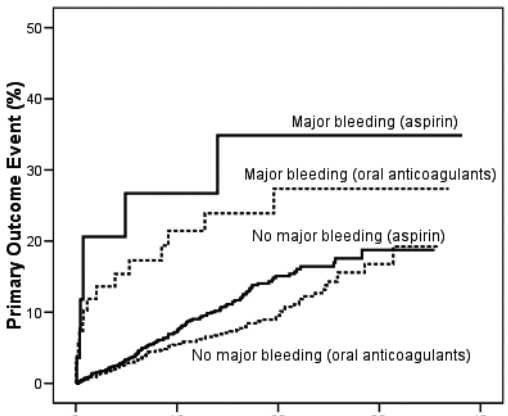


No. at risk	B. (days)				C. (months)				
Time	0	10	20	30	1	10	20	30	40
Major bleeding	101	90	80	73	73	46	26	5	0
No major bleeding	2129	2103	2077	2051	2051	1258	631	94	0

Legend Figure 1. Kaplan-Meier estimates with x-axis time starting at time of index-bleeding and those who did not with x-axis time starting at 9.2 months after randomisation. Panel A represents complete follow-up. Panel B represents the first 30 days of follow-up. Panel C represents 1 to 40 months of follow-up.

For all secondary outcome events, the risks were higher among bleeders than non-bleeders and reached statistical significance for ischaemic stroke and fatal events. The adjusted risk of ischaemic stroke, cardiovascular death, all-cause death, and the composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal ischaemic stroke were ~ 3 to 4 times higher in bleeders than in non-bleeders. The HRs for the primary and secondary outcomes did not differ significantly between patients treated with aspirin and those treated with oral anticoagulants according to the probability values of the interaction terms for bleeding and trial medication (range, 0.16 to 0.95). Figure 2 shows the occurrence of the primary outcome event in bleeders and non-bleeders stratified for trial medication over time.

Figure 2. Kaplan-Meier estimates of cumulative percentages of the primary outcome in patients who experienced a major bleeding and those who did not, stratified for trial medication.

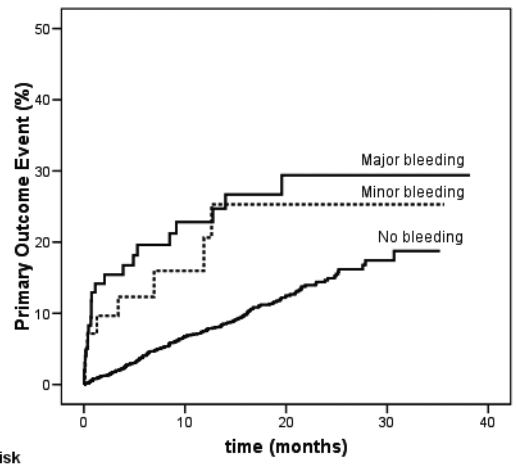


No. at risk					
Aspirin					
Major bleeding	29	10	5	2	0
No major bleeding	1081	626	319	43	0
Oral anticoagulants					
Major bleeding	72	36	21	3	0
No major bleeding	1048	632	312	51	0

Legend. Kaplan-Meier with x-axis time starting at time of indexbleeding and those who did not with x-axis time starting at 9.2 months after randomisation.

If fatal bleedings were included in the primary outcome event, the HRs increased (crude HR, 4.0; 95% CI, 2.8 to 5.9; adjusted HR, 4.0; 95% CI, 2.7 to 5.9). If intracranial bleedings were excluded from the definition of major bleeding, the HRs decreased slightly (crude HR, 2.7; 95% CI, 1.7 to 4.3; adjusted HR, 2.7; 95% CI, 1.7 to 4.4). If intraocular bleedings were excluded from the definition of major bleeding, the results remained essentially the same (crude HR, 3.0; 95% CI, 1.9 to 4.7; adjusted HR, 2.9; 95% CI, 1.8 to 4.6). Minor bleeding showed a trend towards an increased risk of subsequent ischaemic events without reaching statistical significance after adjustment for independent predictors of minor bleeding (crude HR, 2.2; 95% CI, 1.1 to 4.5; adjusted HR, 1.6; 95% CI, 0.8 to 3.4; Figure 3).

Figure 3. Kaplan-Meier estimates of cumulative percentages of the primary outcome in patients who experienced a major or minor bleeding and those without any bleeding.



No. at risk					
Major bleeding	101	46	26	5	0
Minor bleeding	43*	19	10	4	0
No bleeding	2042	1190	575	78	0

Legend. Kaplan-Meier estimates with x-axis time starting at time of indexbleeding and those without any bleeding with x-axis time starting at 9.9 months after randomization. *, Two minor bleedings following a major bleeding were censored, resulting in 43 instead of 45 minor bleedings. None of the minor bleedings were preceded by a major bleeding.

Discussion

Our study in patients with PAD treated with infrainguinal bypass surgery and antithrombotics showed that, like in patients with CAD or cerebrovascular disease, non-fatal major bleeding was a strong and independent predictor for subsequent major ischaemic events, resulting in a 3-fold increased risk for the occurrence of non-fatal myocardial infarction, non-fatal ischaemic stroke, major amputation, or cardiovascu-

lar death. Importantly, this adverse outcome was driven mainly by fatal cardiovascular events.

International guidelines advocate antiplatelets, mainly aspirin, to reduce the risk of secondary vascular ischaemic events in patients with PAD.[4,5] The Dutch BOA Study proved that oral anticoagulants are more effective for the prevention of autologous vein graft occlusion compared with aspirin and tended to be more effective in the prevention of cardiovascular death, myocardial infarction, stroke, and amputation. However, the annual risk of bleeding with aspirin was 2.3% and with oral anticoagulants almost twice as high at 4.1%.[14] The relatively high value of avoiding haemorrhagic complications and the low value of long-term graft patency, in addition to the practical complexity of anticoagulation therapy with vitamin K antagonists, have diminished the widespread recommendation and use of oral anticoagulants in patients with severe PAD treated with vein grafts.[4,5]

The net clinical benefit of antithrombotic treatment depends on the subtle balance between a reduction in the risk of ischaemic events and the inherent bleeding risk. However, this balance is more complicated than previously considered because bleeding seems to be associated with ischaemic consequences. In 40 087 patients from the Global Registry of Acute Coronary Events (GRACE) trial[16] admitted for an acute myocardial infarction, a 2-fold risk of in-hospital death was found in patients with a major bleeding compared with those without a major bleeding.[7] Pooled data of the Organisation to Asses Strategies for Ischaemic Syndromes (OASIS) registry[17], the OASIS-2 study[18], and the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial[19] showed an increased adjusted risk of death (HR, 5.4; 95% CI, 4.0 to 7.3), second myocardial infarction (HR, 4.4; 95% CI, 3.2 to 6.2), and stroke (HR, 6.5; 95% CI, 3.5 to 11.8) within 30 days after bleeding in patients admitted for myocardial infarction.[9] Six months later, patients with bleeding still had a significantly increased risk of in-hospital death (HR, 1.5; 95% CI, 1.0 to 2.4) compared with patients without bleeding. These observations have led to a statement in the latest European Society of Cardiology guidelines for non-ST-segment elevation acute coronary syndromes.[20] The prevention of bleeding is stated to be equally as important as the prevention of ischaemic events because prevention of bleeding is also associated with a significant reduction in the risk for death, myocardial infarction, and stroke. In addition, in patients admitted for ischaemic stroke, gastrointestinal bleeding during hospitalization was independently associated with recurrent stroke, myocardial infarction, venous thromboembolism, and death at six months.[12]

Our findings on predictors, risk, and consequences of bleeding are in accordance with the results in patients with CAD or cerebrovascular disease. Increasing age, hypertension, renal disease, history of stroke, and a history of CAD were repeatedly reported to be independent predictors for bleeding.[7,9,21] In line with previous studies, we found increasing age to be independently related to the risk of major bleeding and identified trends for hypertension, a history of angina pectoris, and of myocardial infarction. We

also found critical limb ischaemia and the use of oral anticoagulants to be independently associated with the occurrence of major bleeding.

No statistical significant differences were seen for the occurrence of ischaemic events after major bleeding between oral anticoagulant- and aspirin- treated groups on the basis of the probability values of the interaction terms for bleeding and trial medication included in multivariable models. Patients allocated to oral anticoagulants had twice as many bleedings compared with patients who used aspirin but had fewer major ischaemic events. With bleeding independently associated with the occurrence of ischaemic events, one would expect patients in the oral anticoagulant group to have more ischaemic events. The observed discrepancy of more bleeding events followed by fewer ischaemic events might be explained by the concurrent effect of oral anticoagulants in preventing ischaemic events. Moreover, the majority of ischaemic events were prevented in patients treated with oral anticoagulants who did not experience a major bleeding. This balance between beneficial and adverse effects of oral anticoagulants has been described in greater detail in our report on the main results of the Dutch BOA Study.[14]

Several hypotheses are suggested to explain the association between bleeding and new ischaemic events. First, bleeding often leads to cessation of antithrombotic therapy. After bleeding, fewer patients admitted with an acute coronary syndrome used antithrombotics at discharge compared with patients without bleeding.[11] The mortality risks were significantly increased among patients who discontinued their aspirin (odds ratio [OR], 7.6; 95% CI, 4.4 to 12.0); thienopyridines (OR, 8.9; 95% CI, 4.4 to 18.1), or unfractioned heparin (OR, 1.9; 95% CI, 1.1 to 3.4) after bleeding compared with those who continued antithrombotic therapy despite bleeding.[11] This would suggest that antithrombotic therapy should be continued after bleeding. In our study, only 20 patients (1%) stopped their antithrombotic treatment as a result of index bleeding. These numbers are too small to draw any conclusions. More research is warranted to study the consequences of discontinued antithrombotic therapy. For now, the main concern is to minimize the patient's increased bleeding risk when given oral anticoagulants by means of intensive international normalized ratio monitoring, avoidance of dual antithrombotic therapy, and thorough screening for vascular risk factors to intensify secondary prevention.

Second, bleeding might indicate that the patient has a more advanced stage of atherosclerosis with fragile blood vessels and is more vulnerable to adverse outcomes. This is supported by the observed dose-related association between the severity of bleeding and ischaemic events (Figure 3).

Other proposed mechanisms include the effects of hypotension, anaemia, and blood transfusion. In our study, 20 patients (1%) received blood transfusion after bleeding, which was too few to assess whether blood transfusion was independently associated with adverse outcomes.

Anaemia was found to be associated with an increased risk of death, repeat revasculari-

sation, or myocardial infarction within 30 days after percutaneous coronary intervention (OR, 1.9; 95% CI, 1.2 to 6.0).[22] At 1 year after percutaneous coronary intervention, anaemia was still significantly associated with higher mortality rates (OR, 1.9; 95% CI, 1.5 to 2. 4[23]; HR, 1.8; 95% CI, 1.3 to 2.3[22]). The risk of ischaemic events and death within 30 days after admission for an acute coronary syndrome appeared to be related to the haemoglobin plasma level.[24]

Blood transfusion was reported to be significantly associated with increased in-hospital (OR, 2.0; 95% CI. 1.1 to 3.2) and 1-year (OR, 1.9; 95% CI 1.4 to 2.5) mortality risk after percutaneous coronary intervention independently of prior bleeding severity but was significantly related to the number of transfusion units (OR, 1.5 per unit transfused; 95% CI, 1.4 to 1).[21] Certain biochemical and immunological effects of stored blood that negatively influence systemic oxygen delivery might partially explain this association. [25-27]

Some limitations apply to our study. Our analyses were posthoc but were applied to a large prospective trial data set. This trial was pragmatic in nature, reflecting normal daily practice, and thus applicable to a wide PAD population. The number of clinical variables collected in the Dutch BOA Study was limited. Therefore, we do not have information on the influence of other potentially relevant variables such as haemoglobin. Major bleeding was defined in the Dutch BOA Study as any non-fatal bleeding requiring hospital attendance regardless of applied treatment. To define major bleeding for the present study in line with the more widely accepted International Society on Thrombosis and Haemostasis criteria,[15] we excluded hospital attendance for epistaxis, haematuria, and menorrhagia and defined them as minor bleedings. Still, the definition of major bleeding by the International Society on Thrombosis and Haemostasis is less stringent and possibly will detect more bleeding episodes than the 2 most frequently applied classifications for major bleeding in cardiology trials defined by the Thrombolysis In Myocardial Infarction (TIMI) and Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) study groups.[28,29] Thus, comparing our results with other studies requires appropriate caution. Finally, studying the consequences of bleeding is limited to an observational study design with methodological challenges because patients with and without bleeding differ in vascular risk factors, resulting in bias caused by confounding, and differ in follow-up time, resulting in survival bias (Table 1). To reduce confounding as much as possible, we adjusted for known differences in risk factors for bleeding in multivariable models. To adjust for survival bias, we equalized the time at risk for ischaemic events in bleeders and non-bleeders in a practical and interpretable manner by starting the follow-up period in non-bleeders 9.2 months after study entry (the mean time between study entry and time of the index major bleeding). Nevertheless, the time scales will never be identical between study groups; therefore, the estimated HRs for determining the impact of bleeding on clinical events should be interpreted with appropriate caution.

These first data in PAD patients are in line with growing evidence that bleeding is independently associated with subsequent death, myocardial infarction, and stroke in patients across the spectrum of atherosclerotic disease. Therefore, optimal antithrombotic treatment should go hand in hand with optimal prevention of bleeding complications. Measures to achieve this include the use of low-dose aspirin and gastrointestinal protection if needed, optimization of treatment compliance, and maintenance of optimal anticoagulant intensity.

Conclusion

We provide the first insight into the independent adverse effect of bleeding on subsequent ischaemic events in a large trial reflecting the general population of patients with PAD treated with oral anticoagulants or aspirin after peripheral bypass surgery. These new findings are in line with evidence in patients with CAD or cerebrovascular disease and call for use of optimal antithrombotic therapy and risk management to effectively reduce ischaemic events meanwhile minimizing the risk of bleeding.

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Chapter 8

Bleeding increases the risk of ischaemic events in patients with peripheral arterial disease. An individual patient data meta-analysis

In preperation

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Abstract

Introduction
Bleeding was found to be associated with an increased risk of new ischaemic events in patients with cardiovascular and cerebrovascular disease. Our aim was to assess the consequences of bleeding in patients with peripheral arterial disease (PAD) treated with antithrombotics and perform subgroup analysis for blood transfusion and discontinuation of antithrombotic therapy.

Methods
Individual patient data of 3701 participants with PAD from the Dutch Bypass and Oral anticoagulants or Aspirin (BOA) Study and the Warfarin Antiplatelet Vascular Evaluation (WAVE) Trial were pooled. Patients had been randomised to oral anticoagulants, antiplatelets, or oral anticoagulants with antiplatelets.
Major bleeding was defined as a non-fatal bleeding in a critical area or organ requiring hospital attendance and occurred over 30 days after surgery. The primary outcome was the composite of lower limb amputation, non-fatal myocardial infarction, non-fatal ischaemic stroke, and death from a vascular cause. Hazard ratios (HR) with 95% confidence intervals (95% CI) were estimated with Cox regression analysis to assess the relationship between bleeding and the primary outcome.

Results
Over a mean follow-up of 15 months 156 patients experienced a major bleeding. The primary outcome occurred in 276 patients of which 28 events were preceded by a major bleeding. Major bleeding was associated with a three-fold increased risk of new ischaemic events (adjusted HR, 2.9; 95% CI, 1.9-4.4).

Conclusion
Major bleeding was found to increase the risk of new ischaemic events considerably in patients with PAD who were treated with antithrombotics. Further research is needed to elucidate the underlying causal mechanisms of this association.

Introduction

Patients with peripheral arterial disease (PAD) are at high risk of ischaemic events, such as lower limb amputation, myocardial infarction, and ischaemic stroke.[1,2] Antithrombotic therapy is highly effective in reducing the risk of ischaemic events, but at the cost of an increased bleeding risk.[3-5] In patients with acute coronary syndromes or an acute stroke bleeding was found to increase the risk of death, myocardial infarction, or stroke.[6-8] Recently, a three-fold increased risk of ischaemic events after major bleeding was found in PAD patients from the Dutch Bypass and Oral anticoagulants or Aspirin (BOA) Study.[9] Several hypotheses have been suggested to explain the association between bleeding and the incidence of new ischaemic events. Bleeding might induce discontinuation of antithrombotic therapy, which in turn leads to an increased risk of ischaemic events.[10] Possibly physiological effects caused by anaemia, or biochemical and immunologic reactions provoked by blood transfusion are responsible for the occurrence of ischaemic events after bleeding.[11-15] Or perhaps this association simply reflects the increased risk of ischaemic events in patients who are at an advanced stage of PAD with severely fragile vessels and therefore bleed more easily.[9]

Our aim was to assess the consequences of bleeding in a pooled data analysis of two large randomised clinical trials with PAD patients who received antithrombotic therapy. A pooled analysis will provide more power yielding a more precise effect-estimate and allows for subgroup analysis of different antithrombotic therapies, blood transfusion, and discontinuation of antithrombotic therapy.

Methods

Study design

The data of the Dutch BOA Study[5] and the Warfarin Antiplatelet Vascular Evaluation (WAVE) Trial[16] were pooled. Between 1995 and 1998, the Dutch BOA Study randomly allocated patients with PAD after infrainguinal bypass surgery to oral anticoagulants (phenprocoumon or acenocoumarol with a target international normalising ratio [INR] between 3.0 and 4.5) or aspirin (daily dose of 80 mg acetylsalicylic acid). Between 2000 and 2003, the WAVE Trial randomly allocated patients with PAD to oral anticoagulants (warfarin or acenocoumarol with target INR between 2 and 3) together with antiplatelet therapy or antiplatelet therapy alone (acetylsalicylic acid with a recommended daily dose between 81 and 325 mg, ticlopidine, or clopidogrel). Only patients diagnosed with acute coronary syndrome or with a coronary stent placement were permitted a dual antiplatelet therapy. Details of both trials were published elsewere.[5,16]

In the present study, PAD was defined as atherosclerosis of the lower extremities with a clinical presentation of disabling intermittent claudication or critical limb ischaemia with rest pain, non-healing ulcers, or focal gangrene. In addition, patients with blue toe syndrome, a previous amputation or arterial revascularization, including thrombolytic therapy, angioplasty, or bypass surgery, were considered to have PAD as well.

At follow-up information on vascular events, other hospital admissions, and compliance with the assigned treatment regimen were recorded. For patients in the BOA trial the follow-up visits took place at three months after bypass surgery and every six months thereafter; for patients in the WAVE trial every three months.

Outcome events

Major bleeding was defined as non-fatal bleeding requiring hospital attendance, irrespective of interventions applied, including bleeding in a critical area or organ, i.e. intracranial, retroperitoneal, gastro-intestinal, haemarthrosis, muscle haematoma, and intraocular bleeding, which largely corresponded with the criteria of the International Society on Thrombosis and Haemostasis (ISTH).[17] Hospital attendance for epistaxis, haematuria, or menorrhagia was defined as a minor bleeding. Fatal bleeding was defined as a bleeding resulting in death within 30 days after bleeding. Any bleeding that occurred within 30 days after surgery was excluded for the current study because these were considered surgery related.

The primary outcome event is the composite of an amputation above the ankle, a non-fatal myocardial infarction, a non-fatal ischaemic stroke, and death from a cardiovascular cause (whichever of the previous events occurred first during the follow-up period). The secondary outcome events are fatal or non-fatal myocardial infarction, fatal or non-fatal ischaemic stroke, amputation above the ankle, death from cardiovascular causes, and death from all causes.

Death from a cardiovascular cause was defined by death primarily attributable to a cardiovascular cause including myocardial infarction, stroke, congestive heart failure, peripheral vascular disease, or other vascular causes, except for bleeding. In addition, cardiovascular death included sudden death or, if no clear data on the cause of death was available, any death for which there was no clearly documented noncardiovascular cause. Myocardial infarction was defined by the presence of at least two of the following three findings: typical ischaemic chest pain, significant elevation of the level of serum creatine kinase, serum creatine kinase MB fraction, or serum troponin, and diagnostic electrocardiographic changes. Ischaemic stroke was defined as a new focal neurologic deficit of sudden onset persisting for more than 24 hours. Strokes were classified as ischaemic or hemorrhagic (including subarachnoid haemorrhage) if a computed tomographic or magnetic resonance imaging scan or an autopsy report was available. Myocardial Infarction was defined by the presence of at least two of the following three findings: typical ischaemic chest pain, elevation of the level of serum specific cardiac enzyme concentrations (e.g. creatine kinase, creatine kinase MB fraction, or troponin), and diagnostic changes on a standard 12-lead electrocardiography. Stroke was defined as a new focal neurologic deficit of sudden onset, persisting for more than 24 hours. Strokes were classified as ischaemic of hemorrhagic (including subarachnoid haemorrhage) if a computed tomographic of magnetic resonance imaging scan or an autopsy report was available. All other strokes were classified as of uncertain cause.

Major amputation was defined as any lower extremity amputation at the ankle or higher performed because ischaemia threatened the viability of the limb.
Both trials were approved by the local Medical Ethics Committee of the principal study center. All participating patients gave written informed consent and their data were processed anonymously. The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

Statistical analysis

Baseline variables with a continuous outcome were summarised as medians and discrete variables as frequencies and percentages. Any missing baseline data were imputed with single linear regression analysis incorporating variables associated with the missing data. If multiple bleedings had occurred, the bleeding which occurred first since randomisation was considered the index bleeding. Baseline characteristics associated with the index bleeding were estimated with univariable Cox regression models and reported as hazard ratio's (HR) with corresponding 95% confidence intervals (CI). Those with a prediction value (P-value) of 0.20 or less were introduced in a multivariable Cox regression model to identify independent predictors for the index bleeding. All models incorporated the index bleeding as dependent variable and baseline characteristics as independent variables with time from study entry to index bleeding or last follow-up.
All outcome events were summarised as frequencies and percentages, and stratified according to patients with or without an index bleeding. To assess whether bleeding was an independent predictor for ischaemic events, the risks of ischaemic events in patients with and without bleeding were compared with HR's and corresponding 95%CI. Crude HR's were derived from univariable Cox regression models, incorporating the primary outcome event as dependent and bleeding as independent variable with time from start date to the first outcome event or last follow-up. Adjusted HR's were calculated by including independent predictors for bleeding into the multivariable Cox regression model.
When analyzing the association between index bleeding and vascular events, the time of index bleeding was considered the start date. To equalize the start date between bleeders and non-bleeders, the start date of non-bleeders was pushed up with the mean time between study entry and index bleeding. Non-bleeders with a total follow-up time that was less than the mean time between study entry and the index bleeding were excluded from further analyses. Furthermore, only outcome events that occurred after the start date were included. Non-fatal ischaemic events that occurred before the start date were considered as medical history and added to the baseline variables for further analyses.
The assumption of proportionality of the hazards for events over time was tested with the Schoenfeld test. To assess whether hazard ratios differed between patients treated with aspirin, oral anticoagulation, or both we calculated the interaction term of bleeding and trial medication. Additional analyses were done for the first 30 days of follow-up and from that time up to last follow-up.

The occurrence of the primary outcome event for patients with and without index bleeding is presented graphically as Kaplan-Meier curves, stratified for trial medication. Sensitivity analyses were performed with and without intracranial and intraocular bleeding included in the definition of non-fatal major bleeding and with and without fatal bleeding included in the definition of vascular death. In addition, subgroup analyses were done for different antithrombotic therapies, blood transfusion, and discontinuation of antithrombotic drugs after bleeding. Lastly, separate analyses were done for minor bleeding.

Table 1. Baseline characteristics among patients with and without major bleeding; differences are expressed as hazard ratio's with 95% confidence intervals (95%CI) with time from study entry to first major bleeding or last follow-up.

Baseline characteristics	Major bleeding present (n=156) No (%)	Major bleeding absent (n=4247) No (%)	Hazard ratio (95% CI)
Demographic factors			
Male sex	103 (66)	2891 (68)	0.9 (0.7-1.3)
Mean age at randomisation	70 (SD ± 10)	67 (SD ± 10)	1.040 (1.023-1.058)
Medical History			
Angina*	38 (24)	929 (22)	1.1 (0.8-1.6)
Myocardial infarction	43 (28)	955 (23)	1.3 (0.9-1.9)
TIA and/or stroke	19 (12)	443 (10)	1.3 (0.8-2.1)
Mean ankle-brachial index (ABI)	0.63 (SD ± 0.33)	0.66 (SD ± 0.31)	0.7 (0.4-1.2)
ABI ≤0.9	131 (84)	3500 (82)	1.1 (0.7-1.8)
ABI ≤0.6	86 (55)	2026 (48)	1.4 (1.0-1.9)
Diabetes Mellitus	52 (33)	1147 (27)	1.4 (1.0-1.9)
Hypertension	82 (53)	1938 (46)	1.3 (0.9-1.8)
Hyperlipidaemia**	48 (31)	1371 (32)	0.9 (0.6-1.3)
Smoking	98 (63)	2757 (65)	0.9 (0.6-1.2)
Critical limb ischaemia	66 (42)	1272 (30)	1.9 (1.4-2.6)
Blue toe syndrome	0 (0)	46 (1)	0.05 (0-39)
Unknown leg status	13 (8)	408 (10)	0.8 (0.4-1.4)
Vascular intervention	87 (56)	1954 (46)	1.5 (1.1-2.0)
Prior medication			
Platelet aggregation inhibitors (PAI)	91 (58)	2746 (65)	0.7 (0.5-0.9)
Oral anticoagulants	42 (27)	1106 (26)	1.1 (0.8-1.6)
No prior medication¥	12 (8)	430 (10)	0.8 (0.4-1.4)
Trial Bypass in BOA (n=2650)			
Femoro-popliteal infragenual	36 (36)	861 (34)	1.0 (0.7-1.6)
Femoro-crural	25 (25)	465 (18)	1.5 (0.9-2.4)
Venous	60 (59)	1486 (58)	1.0 (0.7-1.5)
Trial Medication			
Oral anticoagulants only	72 (46)	1254 (30)	2.1 (1.6-3.0)
PAI and oral anticoagulants	44 (28)	825 (19)	1.5 (1.1-2.1)
PAI only	40 (26)	2168 (51)	0.3 (0.2-0.5)

Legend. SD, standard deviation; TIA, transient ischaemic attack; ACE, angiotensin converting enzyme; *, for one patient data on angina was missing; **, for four patients data on hyperlipidaemia was missing;. ¥, no use of antithrombotics, antihypertensives or statins before trial randomisation.

Results

Patients

The pooled analyses included 4403 patients; 2650 (60%) patients from the Dutch BOA Study and 1753 (40%) patients from the WAVE Trial (patients with atherosclerosis of the carotid or subclavian arteries were excluded). The baseline characteristics of the patients are listed in Table 1. At baseline, 1326 patients were randomly allocated to oral anticoagulants, 869 patients to oral anticoagulants with antiplatelets, and 2208 patients to antiplatelet therapy only.

The mean time between randomisation and non-fatal major bleeding was 12 months (range, 14 hours to 41 months). Patients without non-fatal major bleeding and a total follow-up of 12 months or less (n=693) were excluded from further analyses. The remaining 3710 patients had a mean follow-up of 15 months (range, 14 hours to 39 months). When including minor bleedings, the mean time between randomisation and occurrence of a major or minor bleeding was the same, 12 months (range, 14 hours to 41 months). Patients without any bleeding and a total follow-up of 12 months or less (n=685) were excluded from further analyses. The remaining 3718 patients had a mean follow-up of 15 months (range, 14 hours to 39 months).

Table 2. Types of bleeding per trial medication.

Bleeding characteristics	Oral antico-agulants (n=1015) No (%)	Antiplatelets (n=1858) No (%)	Oral anticoagu-lants and anti-platelets (n=837) No (%)	Total (n=3710) No (%)
Non fatal major bleeding	72 (7)	40 (2)	44 (5)	156 (4)
Gastro intestinal	44 (61)	29 (73)	34 (77)	107 (69)
Retroperitoneal	1 (1)	1 (3)	0 (0)	2 (1)
Intracranial	8 (11)	2 (5)	4 (9)	14 (9)
Intraocular	7 (10)	0 (0)	1 (2)	8 (5)
Haemoptysis	2 (3)	3 (8)	0 (0)	5 (3)
Haemarthros	0 (0)	0 (0)	1 (2)	1 (1)
Muscle haematoma	0 (0)	0 (0)	2 (5)	2 (1)
Other*	10 (14)	2 (5)	0 (0)	12 (8)
Not specified	0 (0)	3 (8)	2 (5)	5 (3)
Non fatal minor bleeding	26 (3)	22 (1)	3 (0.4)	51 (1)
Haematuria	16 (62)	16 (73)	3 (100)	35 (69)
Mennorhagia	2 (8)	0 (0)	0 (0)	2 (4)
Epistaxis	8 (31)	6 (27)	0 (0)	14 (27)
Fatal Bleeding	17 (2)	12 (1)	6 (1)	35 (1)
Gastro intestinal	5 (29)	6 (50)	0 (0)	11 (31)
Retroperitoneal	0 (0)	1 (8)	0 (0)	1 (3)
Intracranial	9 (53)	3 (25)	6 (100)	19 (54)
Haemoptysis	1 (6)	0 (0)	0 (0)	1 (3)
Not specified	2 (12)	2 (17)	0 (0)	3 (9)
Blood Transfusion				
Given in total number of patients	12 (1)	26 (1)	59 (7)	97 (3)
Transfusion units, mean ±SD	3.4 ±2	4.7 ±6	3.4 ±3	3.7 ±4
Given after index bleeding	12 (1)	16 (1)	44 (6)	72 (2)
Transfusion units, mean ±SD	3.4 ±2	4.3 ±5	3.9 ±3	4.0 ±4
Trial medication stopped in total number of patients	89 (9)	101 (5)	150 (18)	340 (9)
after index bleeding	28 (3)	15 (1)	37 (4)	80 (2)

Legend Table 2. *, Haemorrhage outside surgery area (n=11), bleeding occurred after fibrinolysis in a patient who was allocated to antiplatelets (n=1); SD, standard deviation.

Incidence and predictors of major bleeding

A total number of 182 (4.3%) initial major bleeding events occurred, of which 26 were fatal (Table 2). Nine of the initial major bleedings were followed by a second bleeding which was fatal, resulting in a total of 35 fatal bleedings. The majority of the 156 initial non-fatal major bleedings (i.e. index bleeding) were gastro-intestinal bleedings (69%), followed by 14 intracranial bleedings (9%). Most bleedings occurred in patients who were allocated to oral anticoagulants and the least in patients allocated to antiplatelets. Blood transfusions were given in a total of 97 patients who received a mean number of 3.7 transfusion units (standard deviation [SD], 4.3). In 72 patients a blood transfusion was given after index bleeding with a mean number of transfusion units of 4.0 (SD, 3.6). In total 340 (9%) of patients stopped their allocated trial medication, of whom 80 stopped after index bleeding. Patients who were allocated to oral anticoagulants and antiplatelets received most blood transfusions and discontinued their trial medication in the majority of cases.

Patients who experienced an index bleeding were older, more often had an ankle brachial index below 0.6, had critical limb ischaemia with ulcers or gangrene, diabetes, a prior vascular intervention, and were most frequently allocated to oral anticoagulants with or without antiplatelets in comparison with patients without an index bleeding (Table 1). Patients without an index bleeding more often had intermittent claudication without signs of critical limb ischaemia, and were more frequently allocated to antiplatelets compared with patients who did experience an index bleeding. Independent predictors for the index bleeding were age (HR, 1.032 per year; 95% CI, 1.009 to 1.055), critical limb ischaemia (HR, 1.7; 95% CI, 1.1 to 2.5), and the use of oral anticoagulants without antiplatelets (HR, 2.5; 95% CI, 1.6 to 3.8).

Incidence and predictors of minor bleeding

In total 51 initial minor bleedings occurred, of which the majority were haematuria (69%) (Table 2). Two minor bleedings were followed by a major bleeding. No minor bleedings were followed by a fatal bleeding. In eight patients a blood transfusion was given after a minor bleeding, of which two patients were allocated to oral anticoagulants, three patients to antiplatelets, and another three patients to oral anticoagulants with antiplatelets. The mean number of transfusion units given was 2.2 (SD, 2.1). After the occurrence of a minor bleeding 13 patients stopped their allocated trial medication, of which seven patients were allocated to oral anticoagulants, four patients to antiplatelets, and two patients to oral anticoagulants with antiplatelets.

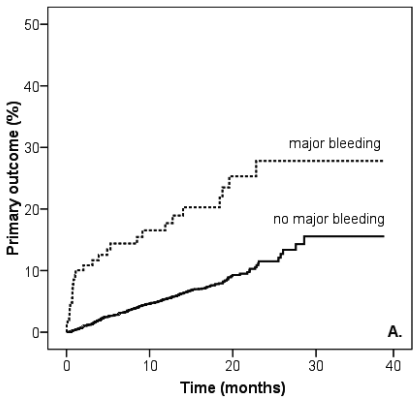
Patients who experienced a minor bleeding were older, were male, more often had an ankle brachial index below 0.6, used oral anticoagulants or did not use antithrombotics, antihypertensives, or statins before randomisation, and were most frequently

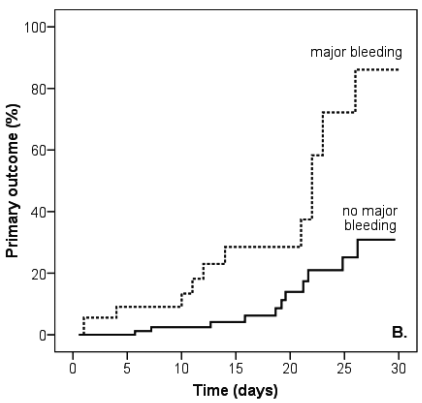
allocated to oral anticoagulants without antiplatelets at randomisation in comparison with patients without a minor bleeding. Patients without a minor bleeding more often were female, used antiplatelets before randomisation, and were more frequently allocated to oral anticoagulants together with antiplatelets at randomisation compared with patients who did experience a minor bleeding.
Independent predictors for minor bleeding were age (HR, 1.071 per year; 95% CI, 1.037 to 1.106), male sex (HR, 2.2; 95% CI, 1.1 to 4.3), the use of antiplatelets before randomisation (HR, 0.5; 95% CI, 0.3 to 0.9), and the use of oral anticoagulants only (HR, 1.9; 95% CI, 1.0 to 3.4).

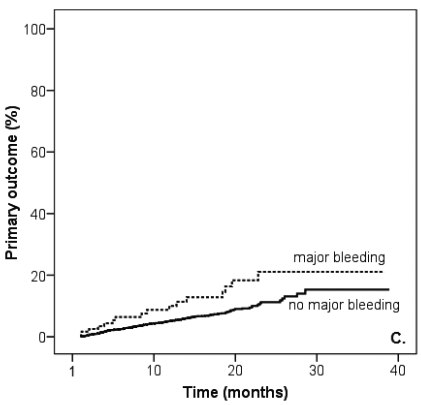
Outcome events and bleeding

The primary outcome event occurred in 276 patients (7%); 83 times (8%) in the anticoagulant group, 149 times (8%) in the antiplatelet group, and 44 times (5%) in the anticoagulant with antiplatelet group (Table 3). A first myocardial infarction occurred in 77 patients, a first ischaemic stroke in 42 patients, a first major amputation in 47 patients, vascular death in 156 patients, and all-cause death in 282 patients.
The mean time between major bleeding and the primary outcome event was 6 months (range, 1 day to 23 months). Of the 156 patients with a non-fatal major bleeding, 28 patients (18%) had a primary outcome event compared with 248 (7%) events in 3544 patients without a major bleeding (crude HR, 3.2; 95% CI, 2.2 to 4.7; Table 3; Figure 1A). After multivariable adjustment, the risk of the primary outcome event remained the same, nearly three times higher in patients with a previous major bleeding versus those without a major bleeding (adjusted HR 2.9; 95% CI, 1.9 to 4.4). Although no violation of proportional hazards was found for the first 30 days after start date (P-value, 0.652) and from 1 to 40 months follow-up (P-value, 0.531), the increased risk of the primary outcome event was mainly present in the first 30 days after bleeding (adjusted HR, 4.2; 95% CI, 1.6 to 10.8; Figure 1B) compared to the risk from 1 to 40 months after bleeding (adjusted HR, 1.7; 95% CI, 1.0 to 2.9; Figure 1C).
If fatal bleedings were included in the definition of the primary outcome event the hazard ratios increased (crude HR, 4.1; 95% CI, 2.9 to 5.8; adjusted HR, 3.6; 95% CI, 2.5 to 5.1). If intracranial bleedings were excluded from the definition of non-fatal major bleeding the hazard ratios decreased slightly (crude HR, 3.0; 95% CI, 2.0 to 4.6; adjusted HR, 2.7; 95% CI, 1.8 to 4.1). If intraocular bleedings were excluded from the definition of major bleeding the risks remained essentially the same (crude HR, 3.1; 95% CI, 2.1 to 4.7; adjusted HR, 2.8; 95% CI, 1.8 to 4.2).
For all secondary outcome events the adjusted risks were three to four times higher among bleeders than non-bleeders and reached statistical significance for myocardial infarction and ischaemic stroke and fatal events (Table 3).

Figure 1. Kaplan-Meier estimates of cumulative percentages of the primary outcome in patients who experienced a major bleeding with x-axis time starting at time of index bleeding and those who did not with x-axis time starting at 12 months after randomisation. Panel A represents complete follow-up. Panel B represents the first 30 days of follow-up. Panel C represents 1 to 40 months of follow-up.







No. at risk	B. (days)						
Time	0	5	10	15	20	25	30
Major bleeding	156	145	141	133	128	122	120
No major bleeding	3554	3540	3525	3504	3484	3470	3457

C. (months)				
1	10	20	30	40
120	76	41	5	0
3457	2685	472	32	0

Table 3. Primary and secondary outcome events in patients with and without a non-fatal major bleeding; differences are expressed as crude and adjusted hazard ratio's (HR) with 95% confidence intervals (95% CI) with time from first major bleeding to first outcome event or last follow-up.

Outcome events (n=3710)	Bleeding present (n=156) No (%)	Bleeding absent (n=3544) No (%)	Crude Hazard Ratio (95% CI)	Adjusted* Hazard Ratio (95% CI)
Primary outcome	28 (18)	248 (7)	3.2 (2.2-4.7)	2.9 (1.9-4.3)
Composite of non-fatal MI, non-fatal IS and vascular death	26 (17)	214 (6)	3.4 (2.2-5.1)	3.0 (2.0-4.6)
Secondary outcomes:				
-amputation	4 (3)	43 (1)	2.6 (0.9-7.3)	1.9 (0.7-5.6)
-myocardial infarction	7 (5)	70 (2)	2.9 (1.3-6.3)	2.9 (1.3-6.5)
-ischaemic stroke	5 (3)	37 (1)	3.9 (1.5-10.0)	4.3 (1.6-11.2)
-vascular death	19 (12)	137 (4)	3.7 (2.3-6.1)	3.1 (1.9-5.0)
-all-cause death	42 (27)	240 (7)	4.9 (3.5-6.8)	3.7 (2.7-5.2)

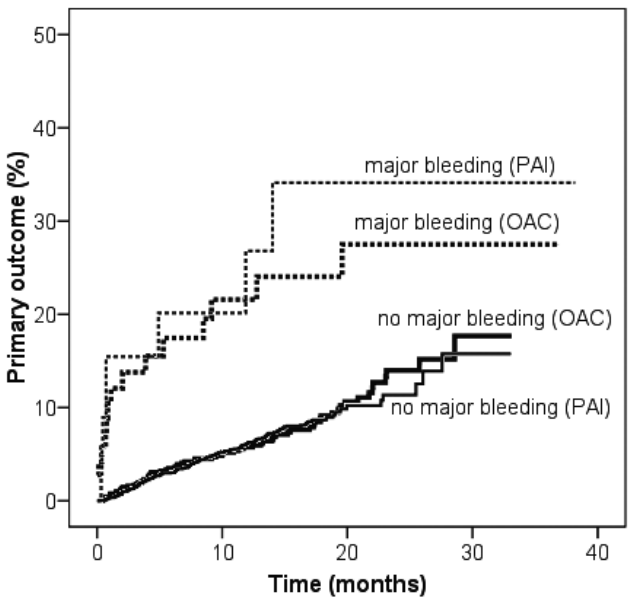
Legend. *, Hazard ratio's adjusted for age, critical limb ischaemia, and the use of oral anticoagulants; MI, myocardial infarction; IS, ischaemic stroke.

The mean time between minor bleeding and the primary outcome event was 5 months (range, 4 days to 13 months). Of the 51 patients with a minor bleeding, 9 patients (18%) had a primary outcome event compared with 260 events (7%) in 3630 patients without a minor bleeding. Minor bleeding showed a trend towards an increased risk of subsequent ischaemic events, without reaching statistical significance after adjustment for independent predictors of minor bleeding (crude HR, 2.9; 95% CI, 1.5 to 5.6; adjusted HR 1.9; 95% CI, 0.9 to 3.8) (Figure 2).

Subgroup analyses

The risk of an ischaemic event after major bleed was higher in patients who used antiplatelets than in patients who used oral anticoagulants (Table 4 and Figure 3). The risk of an ischaemic event after major bleeding was the lowest in patients who used oral anticoagulants and antiplatelets. The hazard ratios for the primary and secondary outcomes did not differ significantly between patients treated with oral anticoagulants, antiplatelets, or both according to the P-values of the interaction terms for index bleeding and trial medication (range, 0.2 to 0.9).

Figure 2. Kaplan-Meier estimates of cumulative percentages of the primary outcome in patients who experienced a major bleeding with x-axis time starting at time of index bleeding and those who did not with x-axis time starting at 12 months after randomisation, stratified for the use of oral anticoagulants (OAC) and platelet aggregation inhibitors (PAI).The third treatment group of OAC and PAI was not included in the figure due to too few primary outcome events for a reliable representation of the survival-curve.



No. at risk					
Time (months)	0	10	20	30	40
Aspirin					
Major bleeding	40	13	6	2	0
No major bleeding	1858	1375	240	15	0
Oral anticoagulants					
Major bleeding	72	36	21	3	0
No major bleeding	1015	545	219	16	0

Table 4. Subgroup analyses according to trial medication for the primary and secondary outcome events in patients with and without a non-fatal major bleeding; differences are expressed as crude and adjusted hazard ratio's (HR) with 95% confidence intervals (95% CI) with time from first major bleeding to first outcome event or last follow-up.

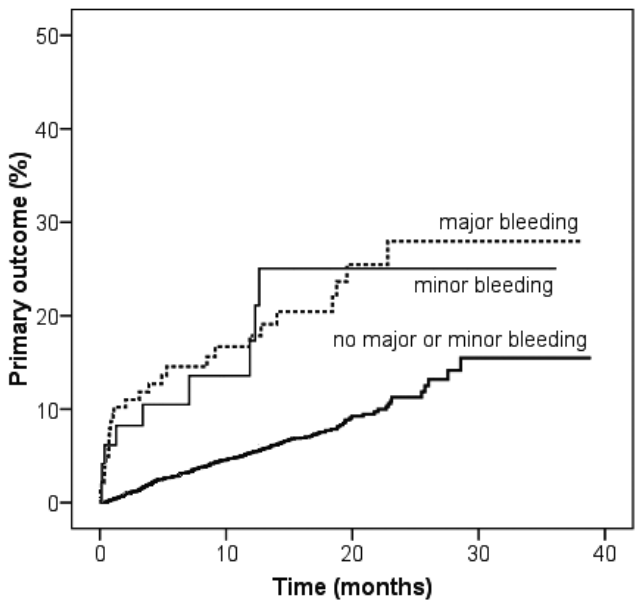
Outcome events (n=3710)	Bleeding present (n=156) No (%)	Bleeding absent (n=3544) No (%)	Crude Hazard Ratio (95% CI)	Adjusted* Hazard Ratio (95% CI)
Oral anticoagulants (n=1015)	n=72	n=943		
Primary outcome	15 (21)	68 (7)	3.1 (1.8-5.4)	2.9 (1.6-4.9)
Composite of non-fatal MI, non-fatal IS and vascular death	14 (19)	54 (6)	3.5 (1.9-6.3)	3.1 (1.7-5.6)
Secondary outcomes:				
-major amputation	3 (4)	18 (2)	2.4 (0.7-8.3)	2.2 (0.6-7.4)
-myocardial infarction	1 (1)	14 (2)	0.9 (0.1-7.3)	0.9 (0.1-6.9)
-ischaemic stroke	2 (3)	5 (1)	5.5 (1.1-28.7)	4.7 (0.9-24.6)
-vascular death	14 (19)	44 (5)	4.4 (2.4-7.9)	3.8 (2.1-7.0)
-all-cause death	26 (36)	91 (10)	3.9 (2.6-6.1)	3.6 (2.3-5.5)
Antiplatelets (n=1858)	n=40	n=1818		
Primary outcome	8 (20)	141 (8)	4.7 (2.3-9.6)	3.7 (1.8-7.7)
Composite of non-fatal MI, non-fatal IS and vascular death	7 (18)	121 (7)	4.6 (2.1-9.8)	3.8 (1.8-8.2)
Secondary outcomes:				
-major amputation	1 (3)	25 (1)	2.9 (0.4-21.5)	2.3 (0.3-16.9)
-myocardial infarction	4 (10)	39 (2)	9.0 (3.2-25.4)	8.1 (2.9-22.8)
-ischaemic stroke	1 (3)	29 (2)	3.1 (0.4-22.7)	2.6 (0.4-19.2)
-vascular death	4 (10)	74 (4)	3.9 (1.4-10.8)	3.2 (1.2-8.8)
-all-cause death	13 (33)	121 (7)	7.9 (4.4-14.3)	6.5 (3.7-11.6)
Oral anticoagulants and Antiplatelets (n=837)	n=44	n=793		
Primary outcome	5 (11)	39 (5)	2.2 (0.8-6.4)	1.9 (0.7-5.6)
Composite of non-fatal MI, non-fatal IS and vascular death	5 (11)	39 (5)	2.2 (0.8-6.4)	1.9 (0.7-5.6)
Secondary outcomes:				
-major amputation	0 (0)	0 (0)	NE	NE
-myocardial infarction	2 (5)	17 (2)	1.8 (0.3-11.1)	1.7 (0.3-11.0)
-ischaemic stroke	2 (5)	3 (0.4)	6.3 (0.7-53.9)	6.7 (0.8-59.7)
-vascular death	1 (2)	19 (2)	1.4 (0.2-10.6)	1.1 (0.1-8.3)
-all-cause death	3 (7)	28 (4)	2.2 (0.6-8.1)	1.9 (0.5-6.7)

Legend. *, Hazard ratio's adjusted for age, critical limb ischaemia, and the use of oral anticoagulants; MI, myocardial infarction; IS, ischaemic stroke; NE, not estimated.

The hazard ratios of an ischaemic event after major bleeding shown in Table 5 were lower in patients who received a blood transfusion than in patients who did not, but did not reach statistical significance because of too few outcome events. According to the P-values of the interaction term for index bleeding and blood transfusion, the hazard ratios for the primary outcome (P=0.004), the composite event of non-fatal myocardial infarction, non-fatal ischaemic stroke, or vascular death (P=0.001), vascu-

lar death (P<0.000), and death of any cause (P<0.000) differed significantly. The hazard ratio of the primary outcome after bleeding decreased when adjusting for blood transfusion and the independent predictors of major bleeding from 2.9 (95% CI, 1.9 to 4.4) to 2.1 (95% CI, 1.0 to 3.7).

Figure 3. Kaplan-Meier estimates of cumulative percentages of the primary outcome in patients who experienced a major or a minor bleeding with x-axis time starting at time of bleeding and those without any bleeding with x-axis time starting at 12 months after randomisation.



No. at risk					
Time (months)	0	10	20	30	40
Major bleeding	156	76	41	5	0
Minor bleeding	49*	25	13	5	0
No bleeding	3513	2654	460	31	0

Legend. * Two minor bleedings following a major bleeding were censored, resulting in 49 instead of 51 minor bleedings. None of the minor bleedings were preceded by a major bleeding.

Table 5. Subgroup analyses according to blood transfusion and trial medication discontinuation for the primary and secondary outcome events in patients with and without a non-fatal major bleeding; differences are expressed as crude and adjusted hazard ratio's (HR) with 95% confidence intervals (95% CI) with time from first major bleeding to first outcome event or last follow-up.

Outcome events (n=3710)	Bleeding present (n=156) No (%)	Bleeding absent (n=3544) No (%)	Crude Hazard Ratio (95% CI)	Adjusted* Hazard Ratio (95% CI)
Blood transfusion (n=97)	n=72	n=25		
Primary outcome	11 (15)	7 (28)	0.7 (0.3-1.8)	0.5 (0.2-1.5)
Composite of non-fatal MI, non-fatal IS and vascular death	10 (14)	7 (28)	0.6 (0.2-1.6)	0.5 (0.2-1.5)
Secondary outcomes:				
-amputation	1 (1)	0 (0)	NE	NE
-myocardial infarction	4 (6)	2 (8)	0.8 (0.1-4.8)	1.1 (0.2-6.3)
-ischaemic stroke	3 (4)	0 (0)	NE	NE
-vascular death	4 (6)	5 (20)	0.4 (0.1-1.5)	0.1 (0.02-1.1)
-all-cause death	9 (13)	7 (28)	0.6 (0.2-1.7)	0.4 (0.1-1.2)
No blood transfusion (n=3613)	n=84	n=3529		
Primary outcome	17 (20)	241 (9)	3.7 (2.3-6.1)	2.9 (1.7-4.8)
Composite of non-fatal MI, non-fatal IS and vascular death	16 (19)	207 (6)	3.9 (2.4-6.7)	3.3 (1.9-5.6)
Secondary outcomes:				
-amputation	3 (4)	43 (1)	3.6 (1.1-11.8)	2.1 (0.6-6.9)
-myocardial infarction	3 (4)	68 (2)	2.4 (0.8-7.7)	2.6 (0.8-8.5)
-ischaemic stroke	2 (2)	37 (1)	3.0 (0.7-12.7)	3.5 (0.8-15.6)
-vascular death	15 (18)	132 (4)	5.6 (3.3-9.7)	3.9 (2.2-6.7)
-all-cause death	33 (39)	233 (7)	7.3 (5.0-10.5)	4.6 (3.1-6.7)
Trial medication stopped after bleeding (n=80)	n=67	n=13		
Primary outcome	11 (16)	1 (8)	2.3 (0.3-17.7)	3.7 (0.4-31.6)
Composite of non-fatal MI, non-fatal IS and vascular death	10 (15)	1 (8)	2.1 (0.3-16.0)	3.9 (0.4-35.2)
Secondary outcomes:				
-amputation	1 (1)	0 (0)	NE	NE
-myocardial infarction	3 (5)	1 (8)	0.6 (0.1-6.1)	0.6 (0.1-5.8)
-ischaemic stroke	3 (5)	0 (0)	NE	NE
-vascular death	5 (8)	0 (0)	NE	NE
-all-cause death	8 (12)	1 (8)	1.8 (0.2-14.2)	2.8 (0.3-25.5)
Trial medication continued after bleeding (n=3630)	n=89	n=3541		
Primary outcome	17 (19)	247 (7)	4.0 (2.4-6.6)	3.2 (1.9-5.3)
Composite of non-fatal MI, non-fatal IS and vascular death	16 (18)	213 (6)	4.3 (2.6-7.2)	3.5 (2.1-5.8)
Secondary outcomes:				
-amputation	3 (3)	43 (1)	3.9 (1.2-12.7)	2.5 (0.7-8.0)
-myocardial infarction	4 (5)	69 (2)	3.6 (1.3-9.8)	3.6 (1.3-10.0)
-ischaemic stroke	2 (2)	37 (1)	3.4 (0.8-14.2)	3.4 (0.8-14.7)
-vascular death	14 (16)	137 (4)	5.6 (3.2-9.7)	3.9 (2.2-6.8)
-all-cause death	34 (38)	239 (7)	8.0 (5.6-11.6)	5.2 (3.6-7.6)

Legend Table 5. *, Hazard ratio's adjusted for age, critical limb ischaemia, and the use of oral anticoagulants; MI, myocardial infarction; IS, ischaemic stroke; NE, not estimated.

The hazard ratios in patients who discontinued antithrombotic therapy after major bleeding were lower than in patients who continued their antithrombotic therapy (Table 5). However, the hazard ratios for the primary and secondary outcomes did not differ significantly between patients who discontinued their antithrombotic therapy according to the P-values of the interaction terms for index bleeding and discontinuated trial medication after index bleeding (range, 0.2 to 0.9). When adjusting for discontinuation of antithrombotic therapy in addition to the independent predictors of major bleeding, the risk of an ischaemic event after bleeding remained fairly unchanged (HR, 3.3; 95% CI, 2.1 to 5.3).

Discussion

This pooled analysis found major bleeding to be a strong and independent predictor of new ischaemic events in patients with PAD who were treated with antithrombotics. The risk of a non-fatal or fatal ischaemic event was three times higher in patients after a major bleeding in comparison with patients who did not experience a major bleeding. This finding concurred with reported risks after bleeding in patients with coronary artery disease and cerebrovascular disease.[6-8,10,18,19]

Atherosclerosis increases the risk of cardiovascular and cerebrovascular ischaemic events, especially fatal ischaemic events.[20] Aspirin and oral anticoagulants reduce the risk of ischaemic events effectively, but also increase the risk of bleeding.[3-5,21-23] In the past few years, the consequences of this adverse effect of antithrombotics have gained more interest by the finding that a non-fatal bleeding was independently associated with subsequent major ischaemic complications in populations with coronary artery disease and cerebrovascular disease.[6-8,10,18,19] Until recently, however, the outcome after bleeding in patients with PAD have not been studied before. Although PAD is an important marker of generalised atherosclerosis, the systemic consequences are still underestimated in comparison with the presence of coronary artery disease and cerebrovascular disease.[24,25] Therefore, we have previously analysed the cohort from the Dutch BOA Study and found that in patients with PAD, as in patients with coronary artery disease and cerebrovascular disease, major bleeding was associated with a threefold increased risk of subsequent ischaemic events (crude HR, 3.0; 95% CI, 1.9-4.6; adjusted HR, 3.0; 95% CI, 1.9-4.7).[9] Now, this finding has been supported by a comparable finding in the pooled data analysis of patients from the Dutch BOA Study and the WAVE Trial (crude HR, 3.2; 95% CI, 2.2 to 4.7; adjusted HR 2.9; 95% CI, 1.9 to 4.4).[5,16]

Identical to the analysis in BOA patients only[9], the independent predictors of non-fatal major bleeding in the present pooled analysis were increasing age, critical limb ischaemia, and the use of oral anticoagulants. Furthermore, we found an ankle-

brachial index below 0.6 and a prior vascular intervention to be associated with an increased risk of major bleeding, instead of the previously reported diabetes and hypertension. Nevertheless, these characteristics were in line with the characteristics found to be associated with major bleeding in the Global Registry of Acute Coronary Events (GRACE).[10] This large multinational registry of patients with acute coronary syndromes reported that patients who experienced a bleeding were older, more frequently had PAD, and were more likely to undergo invasive procedures.[10] This supports the assumption that patients with PAD are at a more advanced stage of atherosclerosis with more fragile vessels which leads to an increased incidence of bleeding and concurrent ischaemic events. Thus, bleeding might be correlated to an advanced stage of atherosclerosis, rather than bleeding induces an ischaemic event. However, after adjustment for the independent predictors of major bleeding, such as age and critical limb ischaemia, the risk of an ischaemic event remained significantly increased after bleeding.

Several hypotheses have been suggested to explain the ischaemic consequences from bleeding. We studied two of the proposed underlying causal mechanisms in our pooled patient data. First, bleeding is likely to lead to discontinuation of antithrombotic therapy which in turn increases the risk of ischaemic events. In GRACE, patients with an acute coronary syndrome who discontinued their antithrombotic therapy after bleeding, had a higher hospital mortality rate than those who continued antithrombotic therapy despite bleeding.[10] However, we did not found an association between discontinuation of antithrombotic therapy and the increased risk of an ischaemic event after major bleeding. This implies that the ischaemic consequences after major bleeding are not so much the result of a clinical action made after bleeding, but more probably are the response to physical reactions after bleeding.

Other proposed mechanisms are the biochemical or immunological effects of a blood transfusion. Stored red blood cells are thought to negatively influence the systemic oxygen delivery by decreasing a patient's nitric oxide level.[11,13,14] Nitric oxide is an endothelium-derived relaxing factor and has an important role in the oxygen exchange.[26] Deprived nitric oxide levels cause vasoconstriction and platelet aggregation.[27] Furthermore, stored red blood cells are low on 2,3-diphosphoglyceric acid and therefore have an increased oxygen affinity which further hinders the oxygen exchange.[28] Lastly, blood transfusions seem to induce inflammatory mediators, such as C-reactive protein which might provoke myocardial ischaemia.[29] Several studies in patients with coronary artery disease reported blood transfusion to be significantly associated with an increased mortality.[11,13] Blood transfusions were mainly given after a retroperitoneal or gastro-intestinal bleeding,[11] as were the blood transfusions in our present study. We also found blood transfusion to be of influence on a patient's outcome, but in the opposite way than previously reported. Instead of increasing the risk of a new ischaemic event, a blood transfusion seemed to reduce the risk of a subsequent ischaemic event. The hazard ratio of the primary outcome after major

bleeding decreased when a blood transfusion was given from 2.9 (95% CI, 1.9 to 4.4) to 2.1 (95% CI, 1.0 to 3.7). Besides the primary outcome, blood transfusions were also significantly associated with the hazard ratios of secondary outcomes, mostly of fatal events. Perhaps, blood transfusions have a protective effect by helping the body to recover more quickly from hypovolemia or anaemia induced by bleeding. Hypovolemia leads to hypoperfusion of the liver and the kidneys which can result in a dysfunction of platelets, impaired clearance of unfractioned heparin or low molecular weight heparin, and abnormalities in the coagulation cascade. Furthermore, a diminished circulating blood volume with a dropped haemoglobin level after bleeding increases the heart rate and the heart's stroke volume to keep peripheral tissue oxygenated. Tachycardia and a prolonged diastole, which reduce the perfusion of the coronary arteries, can lead to myocardial ischaemia with risk of myocardial infarction, heart failure or arrhythmia's. Especially patients with systemic atherosclerotic disease who are likely to have obstructive coronary artery disease and perhaps a history of prior myocardial infarction are at increased risk of an adverse outcome. Anaemia has been shown to be associated with an increased risk of vascular morbidity and mortality.[12,15] So, our opposed finding of a diminished risk of ischaemic events after blood transfusion supports the thought that ischaemic events are provoked by physical reactions activated by bleeding, rather than by clinical actions after bleeding. Regrettably, despite our pooled analysis, we did not have enough data to study the effect of anaemia. However, we did find the risk of ischaemic events to be the highest in the first 30 days after bleeding, when the physical reaction is perhaps the most severe. Furthermore, a bleeding intensity related response was suspected with minor bleeding being associated with a slightly increased risk of subsequent ischaemic events. After adjusting for independent predictors minor bleeding still showed a trend towards an increased risk of subsequent ischaemic events, though without reaching statistical significance.

Lastly, the type of antithrombotic drug seemed to have a binary effect on the risk of an ischaemic event after bleeding. Oral anticoagulants induced most bleedings, but also seemed to more effectively prevent the occurrence of an ischaemic event after bleeding. Although antiplatelets caused less bleedings than oral anticoagulants, the risk of an ischaemic event after a major bleeding was higher in patients who used antiplatelets than in patients who used oral anticoagulants. According to the P-values of the interaction terms for index bleeding and trial medication included in multivariable models, the risk of a ischaemic event after major bleeding did not differ largely between patients treated with oral anticoagulants, antiplatelets, or both antithrombotics. This binary effect was observed in our previous report as well.[9] Also, this binary effect contradicts the assumption that the risk of an ischaemic event is increased by discontinuation of antithrombotic therapy after bleeding, as the risk decreased in the treatment group with most bleedings.

Strengths and limitations

By pooling the data of two randomised controlled trials with comparable populations and a sufficient follow-up period a large homogenous cohort was composed. This pooled cohort represents patients from seven different countries from all over the world and so fairly reflects the general population of PAD patients. In this pooled cohort our previous, single reported increased risk of ischaemic events after major bleeding in patients with PAD from the Dutch BOA Study only was confirmed.[9] More importantly, the present cohort size granted more power and therefore provided more precise effect-estimates than our previous reported findings. In addition, the pooled data allowed for subgroup analyses, which helped to gain more insight in the pathological background of this new finding. Unfortunately our study was limited by the post-hoc analyses which restricted us to use previous applied definitions. In the Dutch BOA Study major bleeding was defined as any non-fatal bleeding requiring hospital attendance, irrespective of the applied treatment.[5] The WAVE Trial handled more detailed criteria to define and categorize bleeding, such as the number of blood products transfused and if the use of warfarin was temporary or permanently discontinued after bleeding.[16] Consensus between the two different bleeding definitions was reached with the more widely applicable and less stringent ISTH criteria.[15] This may have led to the inclusion of more bleeding events than when other classifications were applied, such as defined by the Thrombolysis In Myocardial Infarction (TIMI) and Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) study groups.[30,31] TIMI and GUSTO are the two most often applied classifications for major bleeding in cardiology trials. Thus, comparison of our results with other studies in patients with coronary artery disease and cerebrovascular disease requires appropriate caution.

Furthermore, we came across several methodological issues because studying the consequences of bleeding is only possible in observational study set-up. First, patients with and without bleeding differ in vascular risk factors resulting in bias due to confounding. Second, patients with and without bleeding differ in follow-up time resulting in survival bias. To reduce confounding between the two study groups as much as possible, we adjusted for known differences in risk factors for bleeding in multivariable models. To make the follow-up time between bleeders and non-bleeders comparable, the time of study entry for non-bleeders was set at 12 months past the time of study entry for bleeders, which is the mean time between study entry and time of index bleeding. Conceptually, observation in the two groups now started at an equal (average) time after randomization, rendering two groups that can be compared, also graphically, in a valid fashion. Nevertheless, the time frames between bleeders and non-bleeders will never be exactly the same without randomization. This should be taken into account when interpreting the estimated hazard ratio's for determining the clinical consequences of bleeding.

Conclusion

In patients with PAD who receive antithrombotic therapy major bleeding increases the risk of a new ischaemic event. This risk was independent of the type of antithrombotic treatment given and whether the antithrombotic treatment was stopped because of bleeding. Blood transfusions, however, seemed to decrease this risk of an ischaemic event after bleeding, which has not been reported before. Still, a clear explanation for the association between bleeding and a new ischaemic event in PAD patients has not been found and requires further and preferably fundamental research. Until then, antithrombotic treatment in patients with PAD should be regulated intensely to balance between prevention of ischaemic events and of bleeding events.

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Chapter 9

Summary and general discussion

Objective

This thesis focussed on the long-term prognosis of patients with peripheral arterial disease (PAD) who were treated with infrainguinal bypass surgery. As such, this thesis was not designed to test a hypothesis, but aimed to quantify the risk of ischaemic complications up to 10 years after bypass surgery and elucidate its determinants. The complications recorded were not confined to the affected limb(s) only, but included major ischaemic events which occurred in the whole arterial tree. Herewith, this thesis exceeds earlier studies that primarily assessed procedure related complications (e.g. graft occlusion, re-interventions, lower limb amputation, and short to mid-term survival). In addition, we studied the change in quality of life after peripheral bypass surgery and the use of antithrombotic, antihypertensive, and lipid lowering drugs over the past decade. Evaluation of various ischaemic events together with the patients' perception of health over long-term follow-up resulted in a complete assessment of a patients' clinical prospects after peripheral bypass surgery. This will help improve patient information and prevention therapy. The acquired data on drug use in past and current clinical practice of patients with PAD allowed to detect shortcomings in applied prevention treatments and to raise more awareness of their necessity in PAD patients.

Long-term risks in patients with PAD

PAD is a major public health burden having a high prevalence and an increasing incidence with age.[1-4] PAD is caused by atherosclerosis which gradually leads to narrowing or occlusion of the arteries which supply the lower limbs of oxygenated blood.[5] Yet, the majority of PAD patients is asymptomatic and about one third of patients with PAD experience intermittent claudication during exercise, when ischaemia of the lower limb is provoked.[2,4] These symptoms may progress to critical limb ischaemia with rest pain, ulceration, or gangrene.[5] Infrainguinal bypass surgery is a commonly accepted and widely applied procedure in patients with disabling PAD to relieve pain, improve wound healing, increase limb salvage, and recover and preserve a patients' mobility.[6] However, with progression of PAD the bypass is likely to occlude, possibly requiring re-intervention or lower limb amputation.[7] Furthermore, patients with PAD are at high risk of atherosclerotic manifestations in other arterial beds than in the femoral arterial tract alone, because atherosclerosis is a systemic disease. More often PAD is present together with coronary artery disease or cerebrovascular disease rather than PAD is present on its own, which may lead to myocardial infarction, ischaemic stroke, and death by a vascular cause.[8,9] Nevertheless, in patients after infrainguinal bypass surgery the risks of ischaemic complications other than graft failure and lower limb amputation receive comparatively little attention. In **chapter 2** a systematic review of the literature was performed to evaluate the current knowledge on the overall long-term prognosis, including cardiovascular and cerebrovascular events, of patients after peripheral bypass surgery. The results from 35 selected studies with 28,509 person-years of observation were

pooled to estimate the incidence of non-fatal adverse vascular events, vascular death, non vascular death, and their determinants adjusted for age, sex, and critical limb ischaemia. The incidence of vascular death in patients after peripheral bypass surgery was nearly three times higher than the incidence of non vascular death. The adjusted determinants associated with an increased incidence of vascular death were a study's midyear beyond 1995, renal failure, prior lower limb interventions, critical limb ischaemia, a prosthetic graft, and a distal anastomosis below the knee. Determinants that were associated with a decreased incidence of vascular death were a mean age younger than 66 years, a mean age older than 70 years, a history of cerebrovascular disease, intermittent claudication, and a venous bypass graft. Most determinants we found associated with vascular death corresponded with previously reported determinants.[10,11] Few determinants have not been reported before, such as a study's midyear beyond 1995, a history of cerebrovascular disease, and an age older than 70 years. A twofold increase in the incidence of vascular death between 1995 and 2005 was an unexpected and remarkable finding. Possibly this association reflected the clinical consequences of a growing elderly population and an increasing prevalence of atherosclerotic risk factors in the developed countries. Perhaps it was caused by an observer bias, with studies from the early nineties reporting primarily on graft related outcomes, whereas recent studies also reported on the long-term mortality. Otherwise, we have to conclude that over the past 10 to 15 years the clinical practice has failed to perform prevention treatment adequately in patients with PAD. However, this seems to contradict the assumption that the awareness of PAD being part of a systemic disease has grown over the past decade. So, perhaps there are new, unknown, and therefore untreated risk factors which led to this increased incidence of vascular death and requiring observational studies in large cohorts to be recognised. Other notable findings were the decreased incidence of vascular death in patients older than 70 years and in patients with a history of cerebrovascular disease. Most likely, the increased survival rate in patients over 70 years of age is caused by selection bias within the studies of the pooled analysis, as patients who were at high risk of peroperative morbidity or mortality, such as elderly patients, were probably withheld from bypass surgery. Only elderly patients who were in relatively good health and fit enough for bypass surgery could be included in the study.

Lastly, our pooled analysis was limited by the lack of crude data. The univariable and multivariable Poisson regression analyses were based on the proportions of study characteristics, which may have led to both an underestimation and an overestimation of the associations found. Therefore, these results should be interpreted with some caution and the decreased incidence of vascular death beyond the age of 70 and after a cerebrovascular event might be attributable to chance. To provide more accurate risk estimates of mortality and its determinants in patients after peripheral bypass surgery a meta-analysis is required. Data of non-fatal vascular events could not be adequately analysed as they were scarcely reported. This underlines the need

for more research of other vascular events than of procedure related events alone in PAD patients.

Individual risk assessment in patients with PAD

From the systematic review, discussed in chapter 2, we determined that very few studies have recorded the risk of non-fatal cardiovascular and cerebrovascular ischaemic events in patients after peripheral bypass surgery at long-term follow-up. To gain more insight in the long-term prognosis of these patients a retrospective cohort study was conducted in a sample of patients from the Dutch Bypass and Oral anticoagulants or Aspirin (BOA) Study (**chapter 3**). The Dutch BOA Study was a multicentre randomised trial performed between 1995 and 1998 (77 centres; n= 2690; mean follow-up 21 months) to compare the effect of oral anticoagulants with aspirin in the prevention of infrainguinal bypass occlusion and other ischaemic events.[12] In 482 patients the follow-up was extended from 1998 to 2009. Over a mean follow-up of 7 years, 214 patients had died from a vascular cause, accounting for 67% of all deaths. The primary outcome event was the composite of non-fatal myocardial infarction, non-fatal ischaemic stroke, major amputation, and vascular death, which had occurred in 287 patients (60%). Five years after peripheral bypass surgery more than one third of patients had experienced a primary outcome event, and after 10 years this was more than half of patients. In patients with critical limb ischaemia the risk of a primary outcome event was about two times higher than in patients with intermittent claudication. Other independent determinants of the primary outcome event, besides PAD stage, were increasing age, diabetes, prior vascular interventions, and a femoro-crural bypass. Based on the first four independent determinants a risk chart was developed (Figure 3, page 65). This chart displays the 10-year risks of the primary composite outcome event for each combination of independent determinants. The risks ranged from 25% in patients younger than 65 years of age with intermittent claudication, but without diabetes or a prior vascular intervention to 85% in patients older than 75 years of age with critical limb ischaemia, diabetes, and a prior vascular intervention. With this so called BOA Risk Chart a patients' long-term prognosis can be predicted quickly and effortlessly in the general practitioner's office without the need for any additional testing. This chart facilitates risk stratification of patients after peripheral bypass surgery and so helps the physician to improve patient specific counseling and to set-up an adequate secondary prevention strategy.

Whether a prediction model is to be considered a reliable and accurate tool in clinical practice depends on the methodological and statistical methods applied in the development of the model. One of the important methodological issues for generalisability of a prediction model is patient selection. The patients included in the Dutch BOA Study were derived from 77 medical centres located throughout the Netherlands generating a study population of 2650 participants.[12] The Dutch BOA Study was a pragmatic study with few exclusion criteria including the greater part of the patients

undergoing peripheral bypass surgery between 1995 and 1998. Therefore this study population is a broad reflection of, and thus representative for patients with an indication for peripheral bypass surgery in the Netherlands. For the long-term follow-up study, based on pragmatic reasons, we selected the participants from the hospitals which contributed a large number of patients to the Dutch BOA Study. The number of patients required to develop a stable prediction model was based on the event rate of the primary outcome event in the Dutch BOA Study. Within 7 years, 285 of 482 patients from six of the 77 medical centres were estimated to have experienced a primary outcome event, which was considered sufficiently large according to the rule of thumb that 10 outcome events are required to fit one variable into a multivariable model.[13,14] Eventually we recorded a total of 287 primary outcome events, which was close to the estimated number of 285 events. In addition, 51% of the participants from the Dutch BOA Study had disabling intermittent claudication compared with 52% of the participants selected for follow-up. In both study populations the remaining patients had critical limb ischaemia. We believe this similar distribution suggests these participants are comparable with those of the Dutch BOA Study, and our results are consequently applicable to Dutch patients outside our study with an indication for peripheral bypass surgery.

Other methodological issues affecting generalisability of a prediction model are the relevance of the outcome measure and the execution and completion of the data collection. To the best of our knowledge no other study before has described the long-term prognosis of patients after peripheral bypass surgery by means of a composite outcome event which includes both fatal and non-fatal ischaemic events. Few studies have reported the long-term mortality rates in patients with PAD who underwent infrainguinal bypass surgery.[10,15,16] One study also included non-fatal cardiac events, but was conducted more than 30 years ago, between 1958 and 1988.[16] One recent study developed a risk index for all-cause mortality in patients with an ankle-brachial index of ≤0.9 and another for amputation free survival in patients with critical limb ischaemia after peripheral bypass surgery.[17] However, besides lower limb amputation and fatal vascular events, patients with PAD are also at high risk of non-fatal cardiovascular and cerebrovascular ischaemic events, such as myocardial infarction and ischaemic stroke. In our opinion patients with PAD would benefit the most from the prevention of these non-fatal events.

A limitation of our study was the retrospective data collection. However, the first two years of the data collection were performed prospectively. To minimise the number of missed events the retrospective data collection was done in a stepwise manner according to the proved methods of the LiLAC Study[18], and resulted in only 1% of patients completely lost to follow-up and 6% with a partly incomplete follow-up. A second limitation was the modest discriminatory value of the BOA Risk Chart which was based on the area under the receiver-operator characteristics (AUC-ROC) curves. Compared with the AUC-ROC of models in the LiLAC

Study a similar modest discriminatory value was seen, suggesting that it is difficult to achieve good prognostication for composite outcome events. The best way to assess the discriminatory performance of our model is to validate the model in an independent cohort. However, up till now no cohort in which all ischaemic events were recorded in patients after peripheral bypass surgery over such a time period is available for external validation.

Quality of life in patients with PAD

In daily life the prognosis after peripheral bypass surgery is determined by a patients' perception of health, rather than by clinical risk estimates. The health related quality of life (HR-QoL) in patients with PAD is known to decrease with an increasing severity of lower limb ischaemia.[19-21] Peripheral bypass surgery is able to relieve lower limb complaints and prevent amputation which was shown to significantly improve the HR-QoL in PAD patients up to one year after revascularisation.[22] However, the long-term HR-QoL after peripheral bypass surgery is poorly reported. Therefore, we assessed current HR-QoL scores in PAD patients about 10 years after they underwent peripheral bypass surgery and compared these scores with the HR-QoL scores obtained previously up to two years after surgery. Additionally, the influence of adverse vascular events on the HR-QoL at long-term follow-up was evaluated. The results were discussed in **chapter 6**.

The HR-QoL scores measured shortly after peripheral bypass surgery and measured at long-term follow-up were both substantially lower than the scores measured in the general population at the same mean age. Especially the scores for physical health were lower than average, even if the patients' graft was patent and no other vascular events had occurred during follow-up. Over time and after the occurrence of a vascular event the physical health scores worsened, whereas the scores for mental health and for bodily pain remained more or less the same. No clear explanation could be found for the fairly stable bodily pain and mental health scores. We assumed that perhaps coping mechanisms made the perception of pain become less pronounced over time and enabled patients to mentally adapt to new physical conditions.

When comparing the HR-QoL scores between patients with disabling intermittent claudication and critical limb ischaemia, a slightly different trend between both patientgroups was seen. The HR-QoL assessed shortly after bypass surgery was better in patients with intermittent claudication than in patients with critical limb ischaemia. In patients with intermittent claudication the HR-QoL scores deteriorated at long-term follow-up, while the HR-QoL scores in patients with critical limb ischaemia improved over time, especially the scores for the dimensions pain, social functioning, and mental health. Possibly these higher HR-QoL scores at follow-up are not an actual improvement, but resemble the HR-QoL of long-term survivors who have a better health state than the deceased and the non-responders. However, the considerable increase in the scores of bodily pain, social functioning, and mental health over time

in patients with critical limb ischaemia –scores which had remained more or less stable over time in all PAD patients together– might imply that patients with critical limb ischaemia had applied coping mechanisms at an early stage and eventually benefitted in terms of HR-QoL.
These results help to further understand the changes in a patients' perception of health after peripheral bypass surgery. Previous studies showed peripheral bypass surgery prevented worsening of a patients' HR-QoL on the short term, but cannot prevent the physical health in patients with PAD to deteriorate over time.[23-25] To stabilise the HR-QoL in patients with PAD as long as possible, atherosclerotic risk management through lifestyle modifications and drug treatments might be just as important as surgical intervention.

Medical prevention treatment in patients with PAD

Antithrombotic treatment has proven highly beneficial for bypass patency.[26] Previous studies suggested, and the Dutch BOA Study confirmed that aspirin is especially beneficial for the patency of non-venous peripheral grafts and oral anticoagulants for the patency of venous peripheral grafts.[12,27-29] Before the Dutch BOA Study, in 1992, a survey was performed among Dutch vascular surgeons to inquire after their preferred antithrombotic drug prescriptions in patients after infrainguinal bypass surgery per graft material and graft length.[30] The same survey was repeated shortly after the Dutch BOA Study.[31] Comparison of the results from both surveys showed shifts in the preferred antithrombotic treatment per graft material which were fairly in compliance with the BOA recommendations. Only the decreased preference for oral anticoagulants after venous bypass surgery was against BOA recommendations. This decrease was thought to be brought about by the higher bleeding risk of oral anticoagulants than of aspirin and the difficulties that accompany monitoring the international normalized ratio (INR), which might have made vascular surgeons more reluctant to prescribe oral anticoagulants. Recently, long after the Dutch BOA Study, this survey was distributed again among members of the European Society for Vascular Surgery (ESVS) to evaluate whether the BOA recommendations have been implemented in European clinical practice. The last international survey on antithrombotic treatment after peripheral bypass surgery was conducted nearly 15 years ago.[32] Considering the systemic nature of atherosclerosis, patients with PAD after infrainguinal bypass surgery are not only at risk of bypass occlusion, but also of myocardial infarction, ischaemic stroke, and vascular death.[8,9] These risks remain high long after bypass surgery, as we have seen in chapter 3, and demand durable intensive secondary prevention treatment and an aggressive modification of atherosclerotic risk factors. Fortunately, antithrombotics not only prevent graft occlusion, but also reduce the risk of myocardial infarction, ischaemic stroke, and vascular death.[12,33,34] This has also been seen in PAD patients treated with antihypertensive agents and statins.[35-39] So, in addition, we assessed the vascular surgeons' preference

in antihypertensive and lipid lowering drug treatments and asked for an appraisal of various treatment goals in atherosclerotic risk management. The results of our international survey were described in **chapter 4**.

Overall, the most prescribed antithrombotic drug after bypass surgery was aspirin (50%), followed by oral anticoagulants (22%), and the combination of aspirin and clopidogrel (14%). For venous grafts, 51% of the respondents prescribed aspirin and 26% of the respondents prescribed oral anticoagulants. For prosthetic grafts, 49% prescribed aspirin and 18% prescribed oral anticoagulants. No clear association between the choice of antithrombotic drug and graft material could be distinguished. Between six geographic regions in Europe large differences in preferred antithrombotic treatments per graft type were seen with a far from optimal adherence to international guideline recommendations or evidence from large clinical trials, such as the Dutch BOA Study (Figure 2, page 63). These differences in preferred antithrombotic treatments are possibly explained by guideline recommendations that leave room for personal interpretations. Most guidelines are conservative towards the use of oral anticoagulants because of its higher bleeding risk and practical drawbacks, but do not clearly state an alternative when the effects of antiplatelet therapy are insufficient or how to apply oral anticoagulant therapy safely.[6,40] The guidelines merely suggest to consider treatment with oral anticoagulants per individual who are at high risk of bypass occlusion or of limb loss without specifying the risk factors.[6,40] Lack of a well specified recommendation together with regional differences in social (e.g. patients' level of (dis)comfort and compliance), logistic (e.g. ability for INR monitoring), and economic (e.g. costs and reimbursement) aspects are likely to result in a lack of consensus in antithrombotic treatment throughout Europe.

Besides antithrombotics, also antihypertensives and lipid-lowering drugs are beneficial for secondary prevention in PAD patients.[35-39] Guidelines recommend a systolic pressure below 140 mmHg and a diastolic pressure below 90 mmHg in hypertensive PAD patients.[41-43] Even independent of their blood pressure lowering effect, angiotensin converting enzyme and calcium channel blockers were shown to reduce cardiovascular events in PAD patients.[39,44] Most of our respondents referred patients after peripheral bypass surgery to a cardiologist or vascular internist for blood pressure control, 27% of respondents prescribed antihypertensive agents themselves -mostly angiotensin converting enzyme (ACE) inhibitors-, and 5% did neither. The majority of the respondents (68%) did prescribe statins themselves and only 1% of the respondents did not, without even referring these patients for plasma lipid control elsewhere. Nowadays, statins are indicated for all PAD patients irrespective of their low density lipoprotein (LDL) cholesterol level.[42,45,46] Furthermore, respondents considered complete cessation of smoking and a HbA_{1c} below 7% the most important treatment goals in cardiovascular risk management. Indeed, smoking and diabetes were shown to be the strongest risk factors of PAD.[3] Nevertheless, guidelines favour blood pressure and plasma lipid control above intensive glycaemic control,[6,42,45,46] because in PAD patients the

beneficial effects of a controlled HbA_{1c} are not as convincing on macrovascular level as they are on microvascular level.[47,48] A normal waist circumference was appraised as the least important treatment goal, whereas this measurement for intra-abdominal visceral fat has been shown to be a stronger predictor for the cardiovascular outcome than the body mass index (BMI)[49] which, by the respondents, was considered a more important target for treating overweight.

Despite the modest response rate of 34% (404/1204), the results of this survey provide an indication of the current preference in secondary prevention treatments across Europe. Clearly, the heterogeneity in the applied antithrombotic therapy after infrainguinal bypass surgery implies that there are different opinions on the best treatment regimen whether they are in accordance with level-A evidence or not. Blood pressure and lipid control was applied largely among patients after bypass surgery and mostly conform guideline recommendations, but still a small percentage of patients were deprived of adequate secondary prevention therapy. The appraisal of a few risk management strategies seemed somewhat outdated as recent findings, such as statins which are now known to still have a beneficial effect beyond a normal LDL-cholesterol level[36,37] and the waist circumference which has been identified as a stronger predictor than the BMI[49], were undervalued. Based on these neglects we concluded that the application of secondary prevention therapy can still be improved. This conclusion was supported by the outcome of previous observational studies that patients with PAD who underwent peripheral bypass surgery often do not receive optimal secondary medical prevention.[50–53] Already in 2002, the secretary general of the ESVS emphasised that patients with PAD require a multidisciplinary approach regarding risk factor reduction and secondary medical prophylaxis.[54] He summoned vascular surgeons to take responsibility for their patients' total care and proposed an education programme to update the vascular surgeons' knowledge on secondary medical prevention. A standardized multidisciplinary protocol with flowcharts for decision making on antithrombotic treatment and additional medical prevention and risk management strategies endorsed by the ESVS might stimulate European consensus. To introduce and sustain a complete vascular prevention programme in clinical practice a patients' routine visit to the vascular clinic is believed necessary. Additionally, these repetitive visits might augment a patients' compliance to new lifestyle modifications and medical treatment. To facilitate the increased work load the aid of a physician assistant or nurse practitioner was suggested for patient counselling, perform additional testing, and maintain overview of the secondary prevention applied per patient. In this setting the BOA Risk Chart (Figure 3, page 65) is an excellent tool to help determine the extent of a patients' risk and their need for secondary prevention treatment.

Nevertheless, surveys have a low level of evidence as they provide subjective measurements, which are prone to selection bias. To evaluate the implementation of BOA recommendations in clinical practice objectively, we assessed the actual individual drug

use in patients who underwent peripheral bypass surgery. Data on antithrombotic treatment were collected during the long-term follow-up of patients who participated in the Dutch BOA Study. Again, the changes in antihypertensive and lipid lowering drug treatment over time were recorded as well. **Chapter 5** reports the results of a retrospective drug registration in 478 patients at baseline of the Dutch BOA study, up to two years after the last patient visit in BOA (n=388), and prospectively for patients still alive between 2005 and 2009 (n=209). The data search was restricted to these three time frames, because data collection of drug use is time consuming and inaccuracies are likely to occur due to frequent adjustments in drug prescriptions. Therefore, information on a patients' drug use was not only collected from the treating vascular surgeon and the general practitioner, but also from the pharmacy or the thrombosis services. This resulted in a limited number of patients of whom the drug use could not be completed over the three time frames. In 1% of patients the data on drug use were missing at study baseline, in 7% of patients the data on drug use were missing after the last patient visit in BOA, and in 3% of patients the data on drug use were missing at long-term follow-up.

At baseline of the Dutch BOA Study, only half of patients used antithrombotics. Considering that every patient who was included in this trial required peripheral bypass surgery for disabling PAD, which symptoms develop gradually, all should have started lifelong antithrombotic treatment much earlier. At study entry all patients were randomised between oral anticoagulants and aspirin, which resulted in a large proportion of patients (94%) who still used antithrombotics after the Dutch BOA Study. At long-term follow-up, this proportion remained high at 97%. However, after study completion the BOA recommendations were applied marginally for unknown reasons. Perhaps the allocated trial drug was only changed after a patient experienced an adverse event, such as bleeding or bypass occlusion, and visited the outpatient clinic. Otherwise, in patients without complications who were discharged from follow-up after surgery the BOA recommendations were not carried out. This suggests that patients who do not need to visit the vascular surgeon again, because of good health, eventually do not receive the best antithrombotic treatment. Evidently, publication and presentation of the BOA results, or any other high-level evidence, among vascular surgeons was not enough for their implementation in clinical practice. In the future, to reach as many PAD patients as possible, other physicians should also be informed about new recommendations and stressed to use them, such as cardiologists, neurologists, vascular internists, and the general practitioner.

Before the Dutch BOA Study, the percentages of patients who used antihypertensive and lipid lowering drugs were very low, 49% and 15%, respectively. Although antihypertensive and lipid lowering drug use increased over time, their use remained far from optimal at long-term follow-up. Currently, only two thirds of patients use statins, beta-blockers, or ACE-inhibitors, despite abundant evidence that these treat-

ments are beneficial for secondary prevention in patients with PAD. This underlines the frequently reported undertreatment of patients with PAD.[50-53]
Our trend analyses, however, should be interpreted with caution, because drug use and compliance in survivors might be better than average which might have led to an overestimation of the reported results. Patients still alive at the long-term follow-up of the Dutch BOA Study are most likely to have a relatively lower cardiovascular risk and perhaps received better secondary medical prevention compared with those deceased. Nevertheless, this study provides an extensive overview on drug use in patients with PAD over more than a decade, which to our knowledge, has not been described over such a time period before.

The risk of ischaemic events after bleeding

As discussed earlier, antithrombotics are highly effective in preventing major ischaemic events,[12,33,55] but also increase the risk of bleeding.[12,55] Despite this adverse effect, the prevention of ischaemic events in high risk patients usually tips the scale in favour of antithrombotic treatment. Antithrombotic treatment is indicated in all patients after peripheral bypass surgery.[6,46] Lately, new insights were gained in the consequences of a bleeding event. In 40,087 patients who were admitted with an acute myocardial infarction a statistically significant difference was seen in the number of deaths in the next six months between those who experienced a major bleeding during admission and those who did not (25.7% versus 9.3%; P<0.001).[56] After adjusting for risk factors, such as age, female sex, hypertension, smoking, peripheral arterial disease, a history of prior bleeding, and fibrinolytic therapy, this risk of death remained significantly higher in patients with a major bleeding compared with patients without a major bleeding (hazard ratio [HR], 1.9; 95% CI, 1.6 to 2.2).[56] One year after hospital admission, bleeding still was a strong independent predictor of mortality, indicating that the hospital admission itself did not influence this outcome.[57] Also patients admitted for an ischaemic stroke were at an increased risk of death after bleeding.[58] In addition, bleeding did not only increase the risk of death, but of non-fatal ischaemic events as well.[58] Bleeding complications are reported to lead to a four- to five-fold or even a nine-fold increase in the risk of death, myocardial infarction, or ischaemic stroke during hospital admission and after discharge.[56-60] Although PAD originates from the same pathology as does coronary artery disease and cerebrovascular disease, the association between bleeding and the subsequent increased risk of ischaemic events has not been reported in PAD patients before. Therefore, we studied the effect of bleeding in patients with PAD from the Dutch BOA Study[12] and from the Warfarin Antiplatelet Vascular Evaluation (WAVE) Trial[61] who received oral anticoagulation or aspirin after peripheral bypass surgery.

Chapter 7 describes the first results of bleeding and the risk of subsequent ischaemic events in patients with PAD. Non-fatal major bleeding was found to be a strong

and independent predictor for the composite event of non-fatal myocardial infarction, non-fatal ischaemic stroke, major lower limb amputation, or cardiovascular death (adjusted HR, 3.0; 95% CI, 1.9 to 4.7). These first data in patients with PAD from the Dutch BOA Study[12] are in line with the growing amount of evidence of the adverse outcome following non-fatal bleeding in patients across the spectrum of atherosclerotic disease.[56-60] In **chapter 8** the first and only results in patients with PAD were replicated in a pooled data analysis of patients from the Dutch BOA Study[12] and the WAVE Trial[61], providing more precise effect-estimates. Again non-fatal major bleeding was associated with a three-fold increased risk of new ischaemic events (adjusted HR, 2.9; 95% CI, 1.9 to 4.4). Additionally, subgroup analyses were performed to explore various factors that might be of influence on this new association.

The type of antithrombotic therapy did not seem to influence the association between bleeding and the increased risk of ischaemic events. Although patients who were treated with oral anticoagulants had more bleedings than patients who were treated with antiplatelets, patients with oral anticoagulants experienced less ischaemic events than patients treated with antiplatelets, and vice versa.

Current theories about the the underlying causal mechanisms of this relation between bleeding and the increased risk of ischaemic events are discontinuation of antithrombotic therapy after bleeding, certain biochemical and immunological effects induced by blood transfusion, and the physical effects of hypovolemia, such as hypotension and anaemia. In our pooled data we were able to study two of the proposed theories. After bleeding only 2% of patients discontinued their antithrombotic treatment, which did not affect the risk of an ischaemic event after bleeding substantially. The risk of the primary outcome remained fairly unchanged after adjusting for discontinuation of antithrombotic therapy in addition to the independent predictors of major bleeding (HR, 3.3; 95% CI, 2.1 to 5.3). Moreover, the risk of an ischaemic event after bleeding was higher in patients who continued their antithrombotic treatment than in patients who stopped their antithrombotic therapy. This finding actually contradicted the proposed theory that bleeding possibly leads to cessation of antithrombotic therapy including its concurrent protective effect against ischaemic events. Also, the effect of blood transfusion was opposite to previously reported effects. In patients with an acute coronary syndrome blood transfusion has been found to increase the mortality rate independent of the bleeding event.[62,63] We found a blood transfusion was given in 3% of patients and led to a decrease in the risk of the primary outcome after bleeding (HR, 2.1; 95% CI, 1.0 to 3.7). According to the probability-value of the interaction term for the index bleeding and blood transfusion, the hazard ratio for the primary outcome decreased significantly (P=0.004). Besides the primary outcome, blood transfusions were also significantly associated with the hazard ratios of secondary outcomes, mostly of fatal events. We assumed that a blood transfusion may perhaps have a protective effect by quickly countering the bleeding induced hypovolemia or anaemia.

According to our findings, it seems that the ischaemic consequences after major bleeding are not so much the result of clinical actions made after bleeding, such as stopping antithrombotic therapy or giving a blood transfusion, but are the result of physical reactions activated by bleeding. This assumption was supported by two other findings which concurred with previous reports on the consequecences of bleeding. The risk of an ischaemic event after bleeding was the highest in the first 30 days after bleeding.[56,57] It is likely that the hypovolemia and anaemia and thus the physical reaction to bleeding are the most severe in the first month after bleeding. Furthermore, a bleeding intensity related response was suspected with minor bleeding being associated with a slightly increased risk of subsequent ischaemic events.[60] The more severe the hypovolemia and anaemia, the greater the physical reaction and the risk of ischaemic events.

Despite these assumptions, we are still far from elucidating the causal underlying mechanism of this new association and further research is required. Until then, the prevention of bleeding is equally important as the prevention of ischaemic events. So the primary aim is to seek a balance between reducing a patient's bleeding risk and its risk for ischaemic events in an optimal antithrombotic therapy and an optimal secondary risk management.

Conclusion

In conclusion, PAD is a major public health burden, not only because PAD has a high prevalence and a progressive pathology, but especially because its systemic consequences on the long term are largely underestimated. PAD is an important marker of generalised atherosclerosis, but the long term systemic outcome of PAD does not receive as much attention as the outcome of coronary artery disease and cerebrovascular disease.[51,64] Underestimation of the high risk of ischaemic events in patients with PAD and underestimation of its impact on a patient's daily activities is likely to have resulted in the current undertreatment of patients with PAD which we have observed. Therefore, this thesis intended to increase awareness of the extent of PAD and the severity of its consequences by giving a detailed insight in the course of PAD long after infrainguinal bypass surgery was performed. In addition, we have developed a prediction model for individual risk assessment of major ischaemic events throughout the whole arterial tree in patients with PAD and identified new hazards in their medical treatment. Hopefully, this BOA Risk Chart will help physicians identify those patients with PAD who are at an increased risk of ischaemic events after infrainguinal bypass surgery, improve the information on patients' individual health prospects, and treat them accordingly while taking into account the subtle balance between the benefit and detriment of antithrombotic treatment in the prevention of ischaemic events.

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Chapter 10

Summary in Dutch / Nederlandse samenvatting

Perifeer arterieel obstructief vaatlijden

Pathologie

Perifeer arterieel obstructief vaatlijden is het gevolg van atherosclerose. Atherosclerose, ook wel aderverkalking genoemd, leidt tot het dichtslibben van de slagaderen waardoor de bloedstroom naar de achterliggende weefsels of organen wordt beperkt. Verschillende processen liggen hier aan ten grondslag. Allereerst neemt met de leeftijd de elasticiteit van de slagaderwand af en wordt deze wand stug en dik. Daarnaast is er sprake van een chronisch ontstekingsproces in de vaatwand met als gevolg dat deze dikker wordt en gemakkelijk beschadigd raakt met afzettingen van vet en kalk in de vaatwand. Een ophoping van ontstekingsmateriaal, vet en kalk in de vaatwand wordt een atherosclerotische plaque genoemd. Tenslotte kan de fibreuze kap die de atherosclerotische plaque scheidt van het vaatlumen, scheuren en de inhoud van de plaque in de circulatie terecht komen. Dit materiaal kan samen met de vertraagde stroomsnelheid van het bloed gemakkelijk één of meerdere stolsels (trombi) vormen die distaal het bloedvat geheel afsluiten (occlusie). Bij een afgenomen bloeddoorstroming kunnen klachten van zuurstoftekort in onder meer de benen ontstaan. Echter, perifeer arterieel obstructief vaatlijden in de benen geeft in tweederde van de gevallen geen klachten (asymptomatisch perifeer arterieel obstructief vaatlijden).

Epidemiologie

Perifeer arterieel obstructief vaatlijden komt veel voor bij de algemene bevolking. De prevalentie van patiënten met klachten ten gevolge van perifeer arterieel obstructief vaatlijden varieert tussen de 3% en 11%.[1-4] De prevalentie van patiënten met en zonder klachten van perifeer arterieel obstructief vaatlijden bedraagt ongeveer 30% bij een leeftijd boven de 70 jaar en neemt sterk toe met het stijgen van de leeftijd.[3-5] Het atherosclerotisch proces kan versneld optreden als er sprake is van één of meerdere risicofactoren. Factoren die geassocieerd zijn met het vóórkomen van perifeer arterieel obstructief vaatlijden naast een stijgende leeftijd zijn het negroïde ras[6], het mannelijk geslacht[7,8], roken[9], suikerziekte[10], hoge bloeddruk[11], dyslipidemie[12], een verhoogd *C-reactive protein*[12], een verhoogd fibrine[12], en chronische nierinsufficiëntie[13,14].

Klinisch beeld

De eerste klachten van perifeer arterieel obstructief vaatlijden doen zich in de meeste gevallen voor tijdens inspanning. De klachten zijn het gevolg van een disbalans tussen een gelimiteerde zuurstof toevoer door vernauwde arteriën en een verhoogde metabolische behoefte van de spieren tijdens inspanning. Deze aan inspanning gerelateerde pijn wordt omschreven als een krampende, zeurende of vermoeide sensatie in de spieren van de benen, voornamelijk in de kuiten, welke in rust binnen tien minuten weer afzakt (claudicatio intermittens).[15] In rust wordt de balans tussen de zuurstof

toevoer en de musculaire metabolische behoefte in de benen hersteld. Wanneer de vaatvernauwing een zo vergevorderd stadium heeft bereikt dat deze de balans zelfs in rust verstoort, ontstaan chronisch ischemische rustpijn en niet genezende ischemische huid lesies zoals ulcera of gangreen. Als één of meerdere van deze symptomen langer dan twee weken bestaat, is er sprake van chronisch kritieke ischemie.[16]

Diagnostiek

Bij de anamnese is het van belang de aanzet, lokalisatie, aard, intensiteit, veranderingen over tijd en de duur van de klachten in kaart te brengen. De anamnese kan helpen pijnklachten in de benen te onderscheiden van een neurogene, musculaire of een vasculaire oorzaak. Een positieve anamnese voor claudicatio intermittens kan de verdenking op perifeer arterieel obstructief vaatlijden wekken, maar identificeert geen asymptomatische patiënten met perifeer arterieel obstructief vaatlijden. Bij lichamelijk onderzoek van de onderste extremiteiten let men onder meer op temperatuurverschillen en kleurveranderingen van de huid, spieratrofie, ulcera, gangreen en of de perifere pulsaties beiderzijds palpabel zijn of met behulp van een Doppler hoorbaar zijn. Echter, uiterlijke veranderingen bij inspectie zijn slechts aspecifieke tekenen van perifeer arterieel obstructief vaatlijden. Bij palpabele perifere pulsaties kan de aanwezigheid van perifeer arterieel obstructief vaatlijden in veel gevallen worden uitgesloten, maar andersom niet. Bij non-palpabele perifere pulsaties wordt de aanwezigheid van perifeer arterieel obstructief vaatlijden in veel gevallen overschat. De aangewezen objectieve, snelle en gemakkelijke test voor het diagnosticeren van perifeer arterieel obstructief vaatlijden is het meten van de Enkel-Arm-Index (EAI).[17]

Enkel-Arm-Index

De EAI is een betrouwbare, goedkope en non-invasieve meting met een sensitiviteit die varieert tussen de 61% en 91% en een specificiteit die varieert tussen de 86% en 87% ten opzichte van de gouden standaard, het arteriogram.[18,19] De EAI wordt berekend door de systolische bloeddruk gemeten aan het onderbeen te delen door in rust de systolische bloeddruk gemeten aan de arm.[20] Er is sprake van perifeer arterieel obstructief vaatlijden bij een EAI van 0,9 of lager in rust. Bij normale waarden van de EAI in rust, tussen de 0,91 en 1,4, duidt een afname van 15% tot 20% van de EAI na inspanning op de aanwezigheid van perifeer arterieel obstructief vaatlijden. Deze afname in de EAI samen met inspanningsgerelateerde pijn in de benen bevestigd de diagnose van claudicatio intermittens. Een EAI beneden de 0,5 wordt geassocieerd met een pathologische progressie van perifeer arterieel obstructief vaatlijden, die zich in veel gevallen klinisch manifesteert als chronisch kritieke ischemie. Een EAI boven de 1,4 is verdacht voor niet comprimeerbare verharde bloedvaten ten gevolge van diabetes mellitus, nierinsufficiëntie en andere ziekten die vasculaire calcificatie veroorzaken en vereist alternatieve diagnostiek om de diagnose van perifeer arterieel obstructief vaatlijden te bevestigen, zoals duplex, angiografie, CTA of MRA.[17]

Co-morbiditeiten

Gezien de systemische natuur van atherosclerose komen perifeer arterieel obstructief vaatlijden, coronair vaatlijden en cerebraal arterieel vaatlijden dikwijls gelijktijdig voor. Bij 2% tot 6% van de patiënten met perifeer arterieel obstructief vaatlijden is atherosclerose gelijktijdig symptomatisch in een tweede vaatbed en bij 1% tot 2% van de patiënten in een derde vaatbed.[21] Behalve complicaties aan het aangedane been hebben patiënten met perifeer arterieel obstructief vaatlijden een verhoogd risico op ischemische complicaties van het hart of de hersenen, zoals een myocardinfarct of een herseninfarct met dikwijls een fatale afloop.[21-23] De vijf-jaar incidentie van een myocardinfarct of een herseninfarct bij patiënten met perifeer arterieel obstructief vaatlijden bedroeg respectievelijk ongeveer 10% en 6%.[24] Patiënten met perifeer arterieel obstructief vaatlijden hebben ten opzichte van patiënten met coronair vaatlijden of cerebraal vaatlijden het hoogste risico om te overlijden ten gevolge van een vasculaire oorzaak.[23] Ook patiënten met asymptomatisch perifeer arterieel obstructief vaatlijden hebben een verhoogd risico op een vasculaire dood.[25]

Behandeling

De behandeling van perifeer arterieel obstructief vaatlijden wordt verdeeld in een conservatieve, een medicamenteuze en een invasieve behandeling. Bij een conservatieve behandeling wordt getracht de levensstijl van de patiënt aan te passen om de invloed van aanwezige atherosclerotische risicofactoren te minimaliseren en zo het versnelde proces van atherosclerose te vertragen. Internationale richtlijnen adviseren om pas bij onvoldoende effect van de conservatieve benadering de behandeling uit te breiden naar een medicamenteuze behandeling door geneesmiddelen voor te schrijven.[17,26,27] Indien beide benaderingen niet afdoende zijn om ernstige invaliderende klachten ten gevolge van atherosclerose te verlichten, wordt overgegaan tot een invasieve procedure. In de praktijk en uit de literatuur blijkt dat een simultane benadering vaak geïndiceerd is.

Conservatieve behandeling

Allereerst wordt getracht de klachten van claudicatio intermittens tegen te gaan door met behulp van zogenaamde 'looptraining' de aanmaak en ontwikkeling van nieuwe slagaderen (collateralen) in de benen te bevorderen en daarmee de bloedtoevoer naar het onderbeen uit te breiden. Frequente lichaamsbeweging gedurende minstens 30 minuten, vijf tot zeven keer per week, samen met een verantwoord dieet dat weinig verzadigde vetten bevat, stoppen met roken en afvallen in het geval van overgewicht zijn belangrijke en noodzakelijke aanpassingen van de levensstijl die het schadelijke effect van atherosclerotische risicofactoren reduceren.[17] Hierbij wordt gestreefd naar een *body mass index* (BMI) onder de 25 of een buikomvang onder de 102 cm bij mannen en onder de 88 cm bij vrouwen, een geglycoseerd hemoglobine (HbA_{1c}) onder de 7% bij patiënten met diabetes mellitus, een bloeddruk niet hoger dan 140/90 mmHg of 130/80 mmHg bij patiënten met diabetes of nierinsufficiëntie en een evenwichtige

verdeling tussen lipiden met een triglyceride waarde beneden de 1.7 mmol/L, een *low density lipoprotein* (LDL) cholesterol waarde beneden de 2.6 mmol/L en een high density lipoprotein (HDL) cholesterol boven 1.0 mmol/L bij mannen en boven de 1.3 mmol/L bij vrouwen.[17,26,28,29]

Medicamenteuze behandeling

Ieder medicament dat in staat is de bloeddruk te verlagen is geschikt voor patiënten met perifeer arterieel obstructief vaatlijden en hypertensie.[26] Het type bloeddrukverlager is afhankelijk van de keuze van de behandelend arts wiens overwegingen deels bepaald worden door een patiënt zijn/haar co-morbiditeiten en overig medicatie gebruik.[26] Zowel een *angiotensin converting enzyme* (ACE) remmer als een beta-blokker hebben aangetoond dat zij naast de bloeddruk ook het sterfterisico in patiënten met een atherosclerotische aandoening als perifeer arterieel obstructief vaatlijden of coronair vaatlijden verlagen.[30,31] Enkele internationale richtlijnen adviseren daarom de antihypertensieve behandeling te initiëren met één van deze middelen.[17,27] Andere geschikte bloeddrukverlagers zijn thiaziden, angiotensin-II receptor antagonisten en calciumantagonisten.[32]

De initiële medicamenteuze behandeling van dislipidemie bestaat uit het verlagen van het LDL cholesterol met statinen.[17,33] Fibraten of nicotinezuur zijn effectiever in het verhogen van het HDL cholesterol en het verlagen van triglyceriden dan in het verlagen van het LDL cholesterol. Daarom zijn deze farmaca meer geschikt als aanvulling op het statine gebruik indien de bestaande dislipidemie berust op meer dan een afwijkend LDL cholesterol alleen.[33]

Bij patiënten met diabetes mellitus type II wordt gestart met metformine.[34] Wanneer de bloedsuikerspiegel met metformine alleen onvoldoende onder controle is, wordt insuline of sufonylurea aan de behandeling toegevoegd. Indien de bloedsuikerspiegel nog altijd onvoldoende gereguleerd is, wordt geadviseerd de behandeling met insuline uit te breiden. Andere farmaca die de bloedsuikerspiegel reguleren zijn glinides, alfa-glucosidase remmers, glucagonachtige peptide-1 agonisten, amyline agonisten en dipeptidyl peptidase vier inhibitors.[34]

Tot slot, bloedverdunners, antitrombotica geheten, zijn zeer effectief in het verlagen van het risico op fatale en non-fatale ischemische complicaties in patiënten met perifeer arterieel obstructief vaatlijden.[35-37] Er zijn grofweg twee typen bloedverdunners te onderscheiden: orale antistolling en plaatjesremmers. Orale antistollingsmiddelen remmen de functie van vitamine K. Vitamine K is nodig bij het activeren van verscheidene stollingsfactoren.[38] Plaatjesremmers remmen de adhesie en de aggregratie, het zogezegde samenklonteren van de bloedplaatjes.[39] Om de cardiovasculaire morbiditeit en mortaliteit te verkleinen dienen alle patiënten met perifeer arterieel obstructief vaatlijden langdurig, het liefst levenslang antitrombotica te gebruiken.[17,40,41] Echter, een belangrijk nadelig effect van antitrombotica is de verhoogde kans op bloedingen.[42,43]

Invasieve behandeling

Bij een invasieve behandeling wordt onderscheid gemaakt tussen een beensparende interventie en een amputatie van het aangedane been. Een beensparende interventie bestaat uit een revascularisatie volgens een endovasculaire methode of een chirurgische methode. Onder endovasculaire methoden vallen trombolyse, percutane trombectomie en ballon angioplastiek (i.e. dotteren) met of zonder het plaatsen van een stent. Chirurgische interventies zijn bypass chirurgie, endarteriëctomie, patch angioplastiek of een hybride procedure.[17] Een bypass kan worden vervaardigd van een lichaamseigen ader (i.e. vene) of van een kunststof prothese.

Aspecten die overwogen worden voor het verrichten van revascularisatie of een amputatie zijn de klinische situatie van de patiënt en van het aangedane been, de technische mogelijkheden voor een geslaagde ingreep, het risico van de ingreep in de aanwezigheid van co-morbiditeiten, de verwachte uitkomst van de ingreep, zoals helingtendens van bestaande lesies aan de voet of van de stomp na amputatie, de verwachte duurzaamheid van de reconstructie, het functionele herstel van de patiënt en de verbetering van de kwaliteit van leven.

Revascularisatie met de minder invasieve endovasculaire benadering heeft de voorkeur boven een open chirurgische benadering, aangezien de endovasculaire benadering gepaard gaat met een lagere morbiditeit en mortaliteit op de korte termijn.[44-46] Aangeraden wordt infrainguinale arteriële stenosen tot en met 10 cm in lengte te behandelen met percutane transluminale angioplastiek.[17] Echter, op de lange termijn recidiveren klachten eerder, vinden meer onderbeenamputaties plaats en is het overlevingspercentage lager ten opzichte van een open chirurgische benadering.[44-46] Daarom blijft perifere bypass chirurgie een veel gebruikte methode om de pijnklachten van patiënten te verminderen, wondgenezing te bevorderen, de loopafstand te vergroten en een onderbeenamputatie te voorkomen.[17]

Welke methode van revascularisatie uiteindelijk gehanteerd wordt, hangt af van de anatomische locatie van de obstructie, de lengte van de aangedane arterie, de uitbreiding van atherosclerose in het aangrenzende deel van het vaatstelsel, die de mate van instroom en uitstroom bepaald, de etiologie van de kritieke ischemie, duur van de occlusie, risicofactoren en co-morbiditeiten van de patiënt en de risico's van de procedure, contraindicaties voor één van de methoden en de lokale ervaring in een behandelingsmethode.

Een grote amputatie, onder of boven de knie, is aangewezen bij een zeer uitgebreide, levensbedreigende infectie, oncontroleerbare rustpijn, of wanneer uitgebreide necrose de voet onherstelbaar heeft aangetast. Het doel van een amputatie is om een primaire genezing te bewerkstelligen op een zo distaal mogelijk niveau van de extremiteit voor het behalen van een zo optimaal mogelijke functie en de kans op ambulante zelfstandigheid te vergroten. Veelal kan een amputatie voorkomen worden dan wel uitgesteld, door het adequaat toepassen van pijnbestrijding, wondverzorging en revascularisatie. Wanneer revascularisatie geen klinisch stabiele situatie of functioneel been oplevert en er enkel een lange behandelingsduur verwacht wordt met weinig kans op slagen, kan

primaire amputatie overwogen worden met mogelijk een directe verbetering van de kwaliteit van leven.

Prognose

Het klinisch beloop van claudicatio intermittens is zeer stabiel, ondanks de onderliggende voortschrijdende atherosclerose.[47] Dit is mogelijk te verklaren door de ontwikkeling van collateralen, metabolische adaptatie van ischemische spieren of een aangepaste tred van de patiënt waarbij ischemische spieren zo veel mogelijk ontzien worden. Slechts een kwart van de patiënten zal klinisch ooit significant achteruit gaan. De prognose van patiënten met perifeer arterieel obstructief vaatlijden wordt veelal bepaald door het beloop van bestaande co-morbiditeiten.[48]

Binnen één jaar na angioplastiek van een stenose in de arteria femoralis was bij 23% van de patiënten met claudicatio intermittens de arteriële doorgankelijkheid ter plaatse opnieuw bedreigd. Binnen twee jaar bedroeg dit percentage 34% en binnen vijf jaar 45%.[49] Na angioplastiek van een occlusie van de arteria femoralis bij patiënten met claudicatio intermittens waren deze percentages lager. Binnen één jaar na angioplastiek was de arteriële doorgankelijkheid bij 35% van de patiënten opnieuw gecompromitteerd, binnen twee jaar bij 46% en binnen vijf jaar bij 58%.[49] In patiënten met chronisch kritieke ischemie waren deze percentages nog lager voor zowel stenotische als occluderende lesies.[49] Na angioplastiek met het plaatsen van een stent bleef de arteriële doorgankelijkheid langer gewaarborgd, met name patiënten met chronisch kritieke ischemie hadden hier profijt van.[49]

Na infrainguinale bypass chirurgie trad bij ongeveer een derde van de patiënten met claudicatio intermittens binnen vijf jaar een occlusie van de bypass op. Bij patiënten met chronisch kritieke ischemie was dit ongeveerd de helft.[50-52] Op de lange termijn blijven veneuze bypasses langer doorgankelijk dan kunststof bypasses.[53] Na vijf jaar is rond de 75% van de veneuze bypasses nog open en rond de 45% van de kunststof bypasses met een distale anastomose boven de knie.[54-57]

Veneuze bypasses ontwikkelen stenosen ter hoogte van de kleppen. Kunststof bypasses ontwikkelen veelal hyperplasie van de intima aan de distale anastomose. Een stenose van een veneuze bypass kan na trombolyse met ballon angioplastiek of door chirurgische revisie worden verholpen. Het toepassen van ballon angioplastiek bij een stenose van een kunststof bypass heeft slechts een kortstondig effect op deze rubberachtige lesies, maar trombectomie, patch angioplastiek of het vervangen van de bypass kan worden overwogen.[17]

Slechts 1 tot 3,3% van de patiënten met claudicatio intermittens heeft binnen vijf jaar een grote amputatie ondergaan.[8,58] Binnen één jaar na perifere bypass chirurgie lag het percentage onderbeenamputaties tussen de 10% en 25%.[59] Binnen vijf jaar varieerde dit percentage tussen de 30% en 40% met hogere percentages voor patiënten met chronisch kritieke ischemie.[50,51] Bij chronisch kritieke ischemie komen amputaties en fatale en non-fatale vasculaire complicaties meer voor.

In een jaar tijd stierven van de 100 patiënten met perifeer arterieel obstructief vaatlijden tussen de één en zes patiënten, waarvan één tot drie patiënten stierven ten gevolge van een vasculaire oorzaak.[21,25]
Na vijf jaar is ongeveer 20% van de patiënten met perifeer arterieel obstructief vaatlijden overleden, waarvan tweederde ten gevolge van een vasculaire oorzaak.[24,60,61] Het risico op een vasculaire dood is twee keer zo hoog bij patiënten met symptomatisch perifeer arterieel obstuctief vaatlijden dan bij patiënten met perifeer arterieel obstructief vaatlijden zonder klachten.[62] Hoe lager de EAI des te hoger het riscio op een ischemische complicatie of overlijden al dan niet ten gevolge van een vasculaire oorzaak.[63-65]

Het Nederlands BOA Onderzoek
Infrainguinale bypass chirurgie is een gevestigde behandeling van invaliderende claudicatio intermittens of chronisch kritieke ischemie. Echter, occlusie van een perifere bypass treedt frequent op. Het gebruik van bloedverdunners verlaagt het risico op een bypassocclusie aanzienlijk.[66,67] Aan het begin van de jaren '90 was het echter nog onbekend of orale antistollingsmiddelen of aspirine beter waren ter voorkoming van een bypassocclusie en overige ischemische complicaties. Dit was aanleiding voor het organiseren van het Nederlands Bypass en Orale anticoagulantia of Asprine (BOA) Onderzoek.[68] Het Nederlands BOA Onderzoek werd verricht tussen 1995 en 1998 onder 2690 patiënten uit 77 ziekenhuizen om het effect van orale antistollingsmiddelen en aspirine op het voorkomen van bypassocclusie en ischemische vaatcomplicaties na infrainguinale bypass chirurgie te vergelijken. Na een gemiddelde *follow-up* van bijna twee jaar bleek orale antistolling effectiever in het voorkomen van een veneuze bypassocclusie en aspirine juist effectiever in het voorkomen van een kunststof bypassocclusie. Daarnaast was orale antistolling iets effectiever te zijn voor de preventie van hart- en herseninfarcten, maar dit ging wel ten koste van een grotere kans op bloedingen.

Het vervolg van het Nederlands BOA Onderzoek
Het behoud van de doorgankelijkheid van een bypass in het been op de lange termijn is in de afgelopen decennia veelvuldig bestudeerd, echter gegevens over de lange termijn prognose van patiënten na infrainguinale bypass chirurgie op cardio- en cerebrovasculair gebied zijn beperkt. Hoewel het alom bekend is dat perifeer arterieel obstructief vaatlijden onderdeel uitmaakt van een gegeneraliseerde ziekte waarvan claudicatio intermittens of chronisch kritieke ischemie slechts één van de manifestaties kunnen zijn, wordt de aanwezigheid van overige manifestaties zoals coronair vaatlijden of cerebraal vaatlijden en de mogelijke consequenties daarvan nog altijd onderschat.[69] Met de vergrijzing van de bevolking en de stijgende incidentie van atherosclerotische risicofactoren in de Westerse landen, is het niet onwaarschijnlijk dat patiënten met perifeer arterieel obstructief vaatlijden in de nabije toekomst een groot beroep zullen doen op de zorg. Om de werklast en de kosten in de zorg enigszins te beperken, is een proactieve houding in zowel eerste- als tweedelijns zorg vereist door vroegtijdig een

multidisciplinaire behandeling in te zetten ter preventie van ischemische complicaties bij patiënten met perifeer arterieel obstructief vaatlijden.[70,71] Hiervoor is het ondermeer van belang om te weten waar in de huidige behandelingstrategieën van patiënten met perifeer arterieel obstructief vaatlijden ruimte is voor verbetering, maar bovenal om de behandeling toe te spitsen op het risicoprofiel per patiënt zodat men zorg op maat kan leveren. Deze overwegingen waren aanleiding voor het initiëren van een vervolgonderzoek van het Nederlands BOA Onderzoek met als primair doel om de risico's van grote ischemische complicaties afkomstig uit het gehele arteriële vaatstelsel te kwantificeren en de determinanten daarvan tot tien jaar na infrainguinale bypass chirurgie te bepalen. Daarnaast zijn de veranderingen in het gebruik van antitrombotica, bloeddruk en lipiden verlagende middelen en de verandering van de kwaliteit van leven bij een selectie van de deelnemers van het Nederlands BOA Onderzoek over de tijd gemeten. Het Nederlands BOA *Follow-up* Onderzoek betreft de grootste en omvangrijkste lange termijn studie van patiënten na infrainguinale bypass chirurgie tot dusver.

De lange termijn prognose na infrainguinale bypass chirurgie

Allereerst zijn drie elektronische databases met wetenschappelijke literatuur op een systematische wijze doorzocht om de huidige kennis over de lange termijn prognose van patiënten met perifeer arterieel obstructief vaatlijden na infrainguinale bypass chirurgie in kaart te brengen. In **hoofdstuk 2** zijn de resultaten beschreven van 35 studies die op basis van een aantal vooraf gestelde criteria geselecteerd zijn voor analyse. In totaal bevatten deze 35 studies 8887 patiënten die infrainguinale bypass chirurgie hadden ondergaan met een totale observatie periode van 28509 persoonjaren. Opvallend was dat non-fatale ischemische complicaties zeer beperkt gerapporteerd zijn en dat de aandacht voornamelijk uitging naar bypass gerelateerde complicaties en overlijden na bypass chirurgie. Door dit gebrek aan voldoende gerapporteerde data over non-fatale ischemische complicaties was het niet mogelijk betrouwbare analyses hiervan te verrichten en zijn deze derhalve achterwege gelaten. Wel was het mogelijk de gerapporteerde data betreffende overlijden samen te voegen en een nieuwe incidentie van overlijden te berekenen. De incidentie van overlijden door alle oorzaken bedroeg 8.0 per 100 persoonjaren (95% betrouwbaarheidsinterval, 7.5-8.4). De incidentie van overlijden door een vasculaire oorzaak bedroeg 6.7 per 100 persoonjaren (95% betrouwbaarheidsinterval, 6.2-7.2). Hieruit bleek dat overlijden door een vasculaire oorzaak bijna drie keer meer voor kwam dan overlijden door een non-vasculaire oorzaak (e.g. kanker, infectie, trauma) bij patiënten met perifeer arterieel obstructief vaatlijden na infrainguinale bypass chirurgie. Na 1995 verdubbelde de incidentie van vasculair overlijden ten opzichte van de jaren daarvoor. De incidentie van overlijden door een vasculaire oorzaak was het hoogst tussen de leeftijd van 65 en 70 jaar. Overige studie- of patiëntkarakteristieken die geassocieerd waren met een stijging van de incidentie van vasculair overlijden waren nierfalen, een eerder doorgemaakte vaatinterventie aan

de benen, een vergevorderd stadium van perifeer arterieel obstructief vaatlijden (i.e. chronisch kritieke ischemie), een kunststof bypass en de lengte van de bypass. Het merendeel van deze geassocieerde karakteristieken zijn eerder beschreven in de literatuur.[72,73] Echter, de toegenomen incidentie van vasculair overlijden na 1995 en tussen de leeftijd van 65 en 70 jaar waren nieuwe bevindingen. Mogelijk is de toename in incidentie na 1995 een reflectie van de eerder genoemde vergrijzing en de stijgende incidentie van atherosclerotische risicofactoren in de Westerse landen. Voor een accurate verklaring zal er meer uitgebreid onderzoek moeten plaatsvinden. Aangezien onze analyses gebaseerd waren op proporties die mogelijk hebben geresulteerd in een over- of onderschatting van de werkelijke cijfers, gaat de voorkeur uit naar een meta-analyse die gebaseerd is op individuele patiëntgegevens voor het verkrijgen van meer betrouwbare risicoschattingen.

In **hoofdstuk 3** staat beschreven hoe een predictiemodel is ontwikkeld dat de risico's van zowel fatale als non-fatale ischemische complicaties tot en met tien jaar na perifere bypass chirurgie en de bijbehorende risicofactoren in kaart brengt. Tussen 2005 en 2009 zijn 482 patiënten van zes ziekenhuizen die grote aantallen patiënten hebben geïncludeerd in het Nederlands BOA Onderzoek, retrospectief gevolgd van 1998 tot en met medio 2009. Het primaire samengestelde eindpunt bestond uit een amputatie boven de enkel, een niet-fataal hartinfarct, een niet-fataal herseninfarct, of vasculaire sterfte. Met de Kaplan-Meier methode en Cox regressie zijn jaarlijkse risico's, cumulatieve percentages, en de onafhankelijke risicofactoren van het primaire eindpunt berekend.
De datacollectie was compleet bij 94% van de patiënten. Na een gemiddelde *follow-up* van zeven jaar hebben 287 patiënten (60%) een primair eindpunt doorgemaakt en zijn 323 patiënten (67%) overleden, waarvan 66% door een vasculaire oorzaak. Het cumulatieve percentage patiënten dat het primaire eindpunt had bereikt na één jaar was 11% (95% betrouwbaarheidsinterval, 9-14), 35% (95% betrouwbaarheidsinterval, 31-40) na vijf jaar en 54% (95% betrouwbaarheidsinterval, 50-59) na tien jaar (Figuur 1 op pagina 59). Het gemiddelde jaarlijkse risico op het primaire eindpunt bedroeg 8,3% (95% betrouwbaarheidsinterval, 7,3-9,3). In de eerste acht jaar na bypass chirurgie steeg het jaarlijks risico op het primaire eindpunt geleidelijk van circa 8% naar 9% (Figuur 2 op pagina 63). Het jaarlijks risico op een bypass occlusie daalde in de eerste 5 jaar van 6% naar 2%. Op basis van vier onafhankelijke risicofactoren (leeftijd, diabetes, kritieke ischemie en een vaatinterventie in de voorgeschiedenis) is vervolgens een risico kaart ontwikkeld die systematisch het 10-jaar risico op het primaire eindpunt weergeeft variërend van 25% tot en met 85% (Figuur 3 op pagina 65). Deze zogeheten *BOA Risk Chart* is gemakkelijk te hanteren in de kliniek en biedt de behandelend arts de mogelijkheid door vier eenvoudige vragen te stellen aan de patiënt een nauwkeurige inschatting te maken van de patiënt zijn/haar individuele risico op het doormaken van ischemische complicatie, al dan niet met een fatale afloop, binnen tien jaar na infrainguinale bypass chirugie. Deze kennis stelt de arts in staat de patiënt van

gerichte informatie te voorzien en een individuele behandelingstrategie op te stellen ter preventie van ischemische complicaties.

Veranderingen in medicamenteuze behandelingen over het afgelopen decennium
Om een overzicht te krijgen van de medicamenteuze behandelingen die vaatchirurgen in Europa prefereren voor de preventie van ischemische complicaties bij patiënten met perifeer arterieel obstructief vaatlijden na infrainguinale bypass chirurgie werd een internationaal enquêteonderzoek verricht. De resultaten hiervan staan beschreven in **hoofdstuk 4**. In juni 2007 zijn 1204 leden van de *European Society for Vascular Surgery* uitgenodigd om een digitale enquête in te vullen die online beschikbaar was tot eind april 2008. Naast demografische en werk gerelateerde gegevens werd geïnformeerd welke antitrombotische, bloeddruk en lipiden verlagende medicatie zij bij voorkeur voorschreven aan patiënten na infrainguinale bypass chirurgie. Tot slot werd hen gevraagd dertien verschillende behandelingstrategieën van cardiovasculaire risicofactoren te graderen van minst tot meest belangrijk. De resultaten werden geanalyseerd met behulp van frequentie distributies.
Het deelnemerspercentage bedroeg 34% (403/1204). Het overgrote deel van de deelnemers was man (91%) met een gemiddelde leeftijd van 46 jaar en een gemiddelde praktische ervaring van 16 jaar. Het meest voorgeschreven antitromboticum was aspirine (50%), gevolgd door een orale antistollingsmiddel (22%) en de combinatie van aspirine met clopidogrel (14%) (Figuur 1 op pagina 74). Binnen Europa bestond een grote variatie in de voorkeur voor het soort antitromboticum, waarbij adviezen afkomstig van hoogstaand medisch wetenschappelijk onderzoek in slechts beperkte mate werd nageleefd. De voorkeur voor bloeddruk en lipiden verlagende middelen en de behandelingstrategieën van cardiovasculaire risicofactoren kwamen binnen Europa meer overeen, maar werden niet optimaal toegepast volgens de Europese richtlijnen. Zevenentwintig procent van de vaatchirurgen schreef bloeddruk verlagende middelen voor, voornamelijk ACE-remmers, en 70% lipiden verlagende middelen, voornamelijk statinen. Stoppen met roken werd beoordeeld als de meest belangrijke behandeling van cardiovasculaire risicofactoren en een normale buikomvang werd het laagst gegradeerd (Figuur 3 op pagina 76). Op basis van deze resultaten werd geconcludeerd dat de medicamenteuze behandeling voor de preventie van ischemische complicaties bij patiënten met perifeer arterieel obstructief vaatlijden na infrainguinale bypass chirurgie in Europa onvoldoende was.

Echter, een enquêteonderzoek is zeer onderhevig aan de individuele mening van de deelnemer op dat moment en geeft slechts een subjectieve weergave van de werkelijkheid. Voor een meer objectief overzicht van de toegepaste medicamenteuze behandelingen bij patiënten met perifeer arterieel obstructief vaatlijden na infrainguinale bypass chirurgie is het antitrombotica gebruik van deelnemers van het Nederlands BOA Onderzoek over de afgelopen tien jaar bestudeerd samen met het gebruik van bloeddruk en lipiden ver-

lagende middelen (**hoofdstuk 5**). Dit bood tevens de gelegenheid om na te gaan of de bevindingen van het Nederlands BOA Onderzoek die in 2000 gepubliceerd zijn in *The Lancet* daadwerkelijk geïmplenteerd zijn in de dagelijkse praktijk.
Tussen 2005 en 2009 is het medicatie gebruik bij 482 patiënten afkomstig van zes ziekenhuizen die grote aantallen patiënten hebben geïncludeerd in het Nederlands BOA Onderzoek, retrospectief geregistreerd op drie verschillende tijden: 1) vòòr aanvang van het Nederlands BOA Onderzoek, 2) tot twee jaar na afsluiting van het Nederlands BOA Onderzoek en 3) prospectief tussen 2005 en 2009 (Figuur 1 op pagina 87).
Voor aanvang van het Nederlands BOA Onderzoek werd bij 478 patiënten het medicatie gebruik geregistreerd, waarvan 54% antitrombotica, 49% bloeddruk verlagende middelen en 15% statinen gebruikte (Figuur 2 op pagina 89). Tot twee jaar na het Nederlands BOA Onderzoek werd bij 388 patiënten het medicatie gebruik geregistreerd, waarbij het gebruik van antitrombotica gestegen was naar 94%. Bij 56% van de patiënten met een veneuze bypass werd aspirine gebruikt en bij 44% orale antistollingsmiddelen (Figuur 3 op pagina 90). Vrijwel dezelfde percentages werden gezien in patiënten met een niet-veneuze bypass. Het gebruik van bloeddruk verlagende middelen bedroeg 64% en het gebruik van statinen 40%. Tussen 2005 en 2009 werd bij 209 patiënten het medicatie gebruik geregistreerd, waarvan 97% antitrombotica, 76% bloeddruk verlagende middelen en 65% statinen gebruikten. Bij zowel patiënten met een veneuze als bij patiënten met een niet-veneuze bypasses was het gebruik van aspirine gestegen en dat van orale anticoagulantia gedaald. Dit verschil was het grootst bij patiënten met een niet-veneuze bypass.
Uit de resultaten bleek dat de bevindingen van het Nederlands BOA Onderzoek beperkt zijn nageleefd in de praktijk. Daarnaast was het gebruik van antitrombotica, antihypertensiva en statinen voor aanvang van het Nederlands BOA Onderzoek bij patiënten met symptomatisch perifeer arterieel obstructief vaatlijden laag. Ondanks toename van dit medicatiegebruik in de jaren daarna, bleef het gebruik van bloeddruk verlagende middelen en statinen suboptimaal voor preventie van ischemische complicaties. Deze trend analyse dient echter kritisch geïnterpreteerd te worden, aangezien data op de lange termijn alleen beschikbaar waren van overlevenden die mogelijk een betere behandeling genoten of meer therapietrouw waren dan gemiddeld.

Veranderingen in de kwaliteit van leven over het afgelopen decennium
In de kliniek wordt het succes van perifere bypass chirurgie afgeleid van een gestegen EAI, verlichting van de klachten en toename van de loopafstand, maar uiteindelijk is het de beleving van de patiënt die bepaalt of de ingreep geslaagd is. Uit eerder onderzoek is gebleken dat de kwaliteit van leven bij patiënten met symptomatisch perifeer arterieel obstructief vaatlijden verbetert in het eerste jaar na perifere bypass chirurgie. Echter, de resultaten op de lange termijn zijn onbekend. **Hoofdstuk 6** beschrijft de veranderingen in de kwaliteit van leven tot en met tien jaar na perifere bypass chirurgie en de invloed van doorgemaakte vaatcomplicaties op de kwaliteit van leven.

Tussen 1995 en 1998 is bij 1001 patiënten van het Nederlands BOA Onderzoek de kwaliteit van leven gemeten met behulp van de RAND-36 en de EuroQoL vragenlijst. Tussen 2005 en 2009 zijn patiënten van zes ziekenhuizen die grote aantallen patiënten hebben geïncludeerd in het Nederlands BOA Onderzoek (n=482) retrospectief gevolgd vanaf 1998 tot medio 2009. De patiënten die nog in leven waren, zijn recentelijk benaderd met dezelfde vragenlijsten. Deze recente scores van de kwaliteit van leven zijn vergeleken met de scores verkregen tijdens het Nederlands BOA Onderzoek en met de scores van de algemene Nederlandse bevolking. De kwaliteit van leven wordt beschrijvend bestudeerd en vergeleken met de uitkomsten die bepaald zijn na de infrainguinale bypass chirurgie.

Na een gemiddelde *follow-up* van elf jaar, waren 165 van de 482 patiënten in leven, waarvan 123 (75%) patiënten de RAND-36 en EuroQoL vragenlijst hebben ingevuld. Bij 53 patiënten is de kwaliteit van leven drie keer gemeten: kort na bypass chirurgie, twee jaar na bypass chirurgie, en meer dan tien jaar na bypass chirurgie. Bij hen verslechterde de kwaliteit van leven gedurende de tijd (Figuur 4 op pagina 108). In vergelijk met de Nederlandse bevolking van dezelfde gemiddelde leeftijd waren zowel de recente scores bij 123 patiënten als de scores gemeten tijdens het Nederlands BOA Onderzoek bij 1001 patiënten substantieel lager, zelfs wanneer zij geen vaatcomplicaties hadden doorgemaakt. Na het optreden van een vaatcomplicatie was de kwaliteit van leven aanzienlijk slechter dan wanneer deze niet was opgetreden (Figuur 3 op pagina 107).

De kwaliteit van leven bij patiënten met perifeer arterieel obstructief vaatlijden na infrainguinale bypass chirurgie was slecht en ging in verloop van tijd verder achteruit, ook als zich geen vaatcomplicatie voordeed. Voor het behoud van de kwaliteit van leven bij patiënten met perifeer arterieel vaatlijden is bypass chirurgie alleen onvoldoende en is de behandeling van atherosclerotische risicofactoren, met name het stimuleren van fysieke inspanning, minstens even belangrijk.

Bloedingen verhogen het risico op een ischemische complicatie

Patiënten met perifeer arterieel vaatlijden hebben een verhoogde kans op het doormaken van cardiovasculaire en cerebrovasculaire ischemische complicaties.[21-25] De behandeling met antitrombotica verlaagt deze kans[35-37], maar gaat gepaard met een verhoogd risico op bloedingen.[42,43] Uit onderzoek onder patiënten met coronair vaatlijden is gebleken dat zij die een bloeding doormaakten na het ondergaan van trombolyse of een andere invasieve procedure ter behandeling van een dreigend myocardinfarct een hogere kans hadden op het alsnog doormaken van een hartinfarct of overlijden.[74-77] Ook patiënten met cerebraal vaatlijden hadden na het doormaken van een bloeding een sterk verhoogde kans op ischemische complicaties of overlijden.[78] Ondanks dat patiënten met perifeer arterieel obstructief vaatlijden dezelfde onderliggende aandoening hebben als patiënten met coronair vaatlijden en cerebraal vaatlijden is deze associatie tussen het doormaken van een bloeding en een verhoogde kans op ischemische complicaties niet eerder onderzocht. Daarom is de invloed van een doorgemaakte

bloeding op de kans van het optreden van een ischemische complicatie bij deelnemers van het Nederlands BOA Onderzoek en de vergelijkbare Warfarin Antiplatelet Vascular Evaluation (WAVE) Trial[79] bestudeerd.

Hoofdstuk 7 beschrijft de eerste resultaten van de associatie tussen een doorgemaakte bloeding en de kans op een ischemische complicaties daarna bij patiënten met perifeer arterieel obstructief vaatlijden. Over een gemiddelde periode van 21 maanden zijn bij alle patiënten van het Nederlands BOA Onderzoek (n=2650) 101 non-fatale bloedingen opgetreden, waarvan 60% bij mannen en 71% bij patiënten die orale antistollingsmiddelen gebruikten. Een bloeding werd gedefinieerd als een non-fatale bloeding die meer dan 30 dagen na bypass chirurgie optrad in een belangrijke regio of orgaan (i.e. intracraniaal, retroperitoneaal, gastrointestinaal, intraoculair) waarvoor een ziekenhuisopname geïndiceerd was, met exclusie van bloedingen in het operatiegebied. De voornaamste gebieden voor het optreden van een bloeding waren de tractus digestivus (48%) en intracraniaal (9%). Het samengestelde primaire eindpunt trad op bij 218 patiënten, waarvan bij 22 patiënten het eindpunt vooraf is gegaan door een bloeding. Het primaire eindpunt was een samenstelling van een non-fataal myocardinfarct, een non-fataal herseninfarct of overlijden ten gevolge van een vasculaire oorzaak, inclusief fatale bloedingen. De gemiddelde tijd tussen het optreden van een bloeding en het primaire eindpunt bedroeg 4 maanden. Het doormaken van een bloeding was significant geassocieerd met het optreden van het primaire eindpunt (hazard ratio [HR] 3,0; 95% betrouwbaarheidsinterval, 1,9-4,6). Ook na correctie voor onafhankelijke risicofactoren van bloedingen bleef deze associatie significant verhoogd (hazard ratio [HR] 3,0; 95% betrouwbaarheidsinterval, 1,9-4,7). Onafhankelijke risicofactoren voor het doormaken van een bloeding waren het stijgen van leeftijd, het gebruik van orale antistollingsmiddelen, en chronische kritieke ischemie.
De bevinding in hoofdstuk 7 werden bevestigd door een tweede analyse in een grotere patiëntengroep, die staat beschreven in **hoofdstuk 8.** Bij 3701 deelnemers van het Nederlands BOA Onderzoek en the WAVE Trial tezamen werd opnieuw een drie keer verhoogde kans op een ischemische complicatie na het doormaken van een bloeding gevonden (gecorrigeerde HR, 2.9; 95% CI, 1.9 to 4.4). Het voordeel van een grotere patiëntengroep is dat de uitkomsten van de statistische analyses meer betrouwbaar zijn en dat het ruimte biedt voor subgroep analyses. Deze subgroep analyses kunnen meer inzicht verschaffen in de onderliggende causale mechanismen van deze nieuwe associatie. Uit de subgroepanalyses bleek het type antitrombotica niet van invloed te zijn op de gevonden associatie. Hoewel het gebruik van orale antistollingsmiddelen gepaard ging met een hogere kans op bloedingen dan bij het gebruik van aspirine, was de kans op een ischemische complicatie na bloeden juist lager ten opzichte van de kans na bloeden bij aspirine gebruik. Dit wordt mogelijk verklaard door het feit dat orale antistollingsmiddelen effectiever zijn in het voorkomen van ischemische complicaties dan aspirine[43,68], wat een deel van het verhoogde risico op een ischemische

complicatie na bloeden opheft. Ook het stoppen van de antitrombotica behandeling na het doormaken van een bloeding (2%) was niet van invloed op de gevonden associatie. Het toedienen van een bloedtransfusie geschiedde bij 3% van de patiënten na het doormaken van een bloeding en reduceerde het risico op een ischemische complicatie. Dit is in tegenstelling met eerder gerapporteerde resultaten waarbij het toedienen van een bloedtransfusie juist het risico op een ischemische complicatie verhoogd. Gesuggereerd wordt dat een bloedtransfusie biochemische of immunologische reacties opwekt die de zuurstof transport naar de organen bemoeilijken of het atherosclerotische ziekteproces verergeren.[80-86] Onze veronderstelling is dat de hemodynamische gevolgen na een bloeding aanleiding zijn voor het uitlokken van ischemie. Bloedverlies kan leiden tot een daling van het bloedvolume en van de bloeddruk met als gevolg dat er vasoconstrictie optreedt met een verminderde weefselperfusie en de hartslag stijgt wat een extra belasting is voor het hart. Deze hypothese wordt gesterkt door de volgende bevindingen. De kans op een ischemische complicatie was het hoogst in de eerste 30 dagen na het optreden van een bloeding, de periode waarin de hemodynamische gevolgen van het bloeden op z'n hevigst zijn. Er is een relatie gevonden tussen de mate van bloeden en de grootte van het risico. Hoe groter de bloeding, des te hoger het risico op een ischemische complicatie. Tot slot reduceert een bloedtransfusie het risico op het doormaken van een ischemische complicaties, mogelijk doordat het het bloedverlies corrigeert en het bloedvolume weer op peil brengt.
Ondanks deze hypothesen zijn we nog verre van het ontrafelen van de werkelijke mechanismen die ten grondslag liggen aan de associatie die gevonden is tussen bloeden en het optreden van ischemische complicaties. Totdat hier meer onderzoek naar is verricht, is het voorkomen van ischemische complicaties even belangrijk als het voorkomen van bloedingen

Conclusie

In dit proefschrift staat de lange termijn prognose van patiënten met perifeer arterieel obstructief vaatlijden centraal. Perifeer arterieel obstructief vaatlijden maakt deel uit van een aandoening die het gehele arteriële vaatstelsel aantast. Daarom wordt de prognose van patiënten met perifeer arterieel obstructief vaatlijden niet alleen bepaald door complicaties aan de benen, maar ook door complicaties elders in het lichaam. In dit onderzoek is daarom de aandacht tevens uitgegaan naar cardio- en cerbrovasculaire complicaties.
Uit de wetenschappelijke literatuur komt duidelijk naar voren dat patiënten met perifeer arterieel obstructief vaatlijden na infrainguinale bypass chirurgie een zeer hoge kans hebben op overlijden en met name ten gevolge van een vasculaire oorzaak. Echter, de lange termijn gegevens over non-fatale ischemische complicaties na infrainguinale bypass chirurgie zijn beperkt gerapporteerd, evenals de kwaliteit van leven. Met het vervolgonderzoek van het Nederlands BOA Onderzoek zijn de risico's op verschillende non-fatale en fatale vasculaire complicaties, alsmede de risicofactoren

voor het optreden van deze complicaties op lange termijn na infrainguinale bypass chirurgie voor het eerst in kaart gebracht. Aan de hand van deze resultaten is een risico scoringskaart ontwikkeld waarmee het risicoprofiel per patiënt nauwkeurig, snel en eenvoudig kan worden ingeschat. Een persoonlijk risicoprofiel helpt om per patiënt de behandeling ter preventie van ischemische complicaties in de toekomst aan te scherpen. Mogelijk helpt dit risicoprofiel ook om de uitgebreidheid van de onderliggende vaataandoening opnieuw bij de behandelend arts onder de aandacht te brengen en de noodzaak van een optimaal medicamenteus beleid te onderstrepen, dat bij evaluatie enige tekortkomingen toonde. Met de nieuwe inzichten in de gevolgen van bloeden is het van belang de juiste balans te vinden in het voordelig en nadelig effect van antitrombotica. En voor het behoud van de kwaliteit van leven bij patiënten met perifeer arterieel obstructief vaatlijden zijn conservatieve behandelingstrategieën minstens even belangrijk.

Woordenlijst

Anamnese	het opnamegesprek, het inwinnen van informatie bij de patiënt
Anastomose	een kunstmatige of natuurlijke verbinding van bloedvaten of delen van het spijsverteringskanaal
Angiogram/Arteriogram	een techniek waarbij de bloedvaten worden afgebeeld door tijdens beeldvorming (meestal röntgenstraling) contrastvloeistof in een slagader te spuiten.
Antitrombotica	bloedverdunnende middelen, een overkoepelende term voor alle soorten bloedverdunners, inclusief antistollingsmiddelen en plaatjesremmers.
Arterie	slagader
Atherosclerose	slagaderverkalking, het dichtslibben van de slagaderen door afzettingen van vet, kalk, bindweefsel en stolsel tegen de binnenkant van de vaatwand in combinatie met het verdikken van de vaatwand door groei en een ontsteking in de vaatwand
Bypass	omleiding, omlegging, overbruggingsoperatie
Cerebraal	met betrekking tot de hersenen
Circulatie	boeddoorstroming
Coronair	met betrekking tot de kransslagader(s)
C-reactive protein	een eiwit dat in de acute fase van een onderliggende systemische inflammatie/ontsteking onmiddellijk reageert en daarom als nauwkeurige marker fungeert
CTA	Computer Tomografie Angiografie . Een techniek waarbij de bloedvaten worden afgebeeld door tijdens beeldvorming contrastvloeistof in een slagader te spuiten. Meestal wordt als beeldvorming röntgenstraling gebruikt, waarbij een 2-D afbeelding van de vaten ontstaat. De afbeelding wordt een angiogram of arteriogram genoemd. Met behulp van CT kan een 3-D afbeelding worden vervaardigd die CTA wordt genoemd.
Diabetes mellitus	suikerziekte
Dislipidemie	een verstoorde samenstelling van de cholesterolhuishouding
Distaal	uiteinde, het verst verwijderd van het centrum of de oorsprong
Doppler-onderzoek	Onderzoek naar de snelheid van de bloedstroom en de stroomrichting van het bloed in een slagader of ader, waarbij gebruik gemaakt wort van ultrageluidsgolven die voor de

mens niet hoorbaar zijn. De geluidsgolven worden uitgezonden door een transducer die op de huid wordt geplaatst. Deze tranducer is tegelijk ook de ontvanger van de golven die teruggekaatst worden. Het bloed bevat ontelbare bloedlichaampjes die geluidsgolven kunnen terugkaatsen. De teruggekaatste geluidsgolven zijn wel hoorbaar. Afhankelijk van de stroomsnelheid van het bloed wordt er een hoger of lager geluid weergegeven. Dit noemt men het Doppler-effect. Als het bloed veel sneller stroomt, is er een vernauwing. Als er geen stroom wordt waargenomen, is het bloedvat verstopt. Wanneer het Doppler-onderzoek wordt gecombineerd met een echografie spreken we van een Duplex-onderzoek.

Duplex-onderzoek — Duplex betekent letterlijk dubbel. Het duplex-onderzoek is een onderzoek waarbij Doppler-onderzoek en echografie gecombineerd worden. Een ander woord voor duplex-onderzoek is echo-Doppler-onderzoek. Echografie en Doppler zijn verenigd in één toestel. De echografie wordt gebruikt om de bloedvaten in beeld te brengen. Het Doppler-onderzoek wordt gebruikt om de snelheid van de bloedstroom te meten met behulp van geluidsgolven. Met duplex-onderzoek is deze stroomsnelheid niet alleen hoorbaar maar wordt deze ook zichtbaar gemaakt op een beeldscherm. Het ziet eruit als een golfbeweging. De golfbeweging is een weergave van de toename en afname van de stroomsnelheid van het bloed, onder invloed van de hartslag. Met het duplex-onderzoek kunnen slagaders, aders en het hart in beeld gebracht worden. De precieze plaats en de ernst van de problemen kunnen goed bepaald worden met deze onderzoeksmethode.

Epidemiologie — de leer van de frequentie van het optreden van een ziekte en van factoren die de frequentie bepalen

Etiologie — de leer der ziekte-oorzaken

Fibrine — een vezelig, onoplosbaar eiwit dat bij stolling wordt gevormd uit fibrinogeen

Gangreen — afgestorven weefsel, necrose, koudvuur

Genuaal — met betrekking tot de knie

Hemoglobine — de ijzerhoudende kleurstof van de rode bloedcellen die bindt met zuurstof

Hypertensie — hoge bloeddruk

Incidentie — het aantal nieuwe gevallen van een ziekte dat in een omschreven populatie in een omschreven periode optreedt

Infarct — weefselschade dat is ontstaan na zuurstoftekort.

Infrainguinaal	onder de lies
Inguinaal	met betrekking tot de liesstreek
Intracraniaal	binnen de schedel
Intraoculair	binnen het oog
Ischemie	gebrek aan zuurstof
Musculair	de spieren betreffend
Myocard	hartspier
Myocardinfarct	hartinfarct, hartaanval.
MRA	*Magnetic Resonance Angiogram*. Een techniek waarbij de bloedvaten worden afgebeeld door tijdens beeldvorming contrastvloeistof in een slagader te spuiten. Meestal wordt als beeldvorming röntgenstraling gebruikt, maar wanneer als beeldvorming een magnetisch veld wordt toegepast noemt men dit een MRA.
Neurogeen	met betrekking tot het zenuwstelsel
Neuropathie	een aandoening van het zenuwstelsel
Morbiditeit	de mate van invaliditeit naar aanleiding van een ziekte
Mortaliteit	de mate van sterfte naar aanleiding van een ziekte
Occlusie	een afsluiting
Perifeer	uiteinde , aan de buitenzijde
Prevalentie	het aantal bestaande gevallen van een ziekte dat in een omschreven populatie in een omschreven periode voorkomt
Prognose	de voorspelling omtrent het verdere beloop van een ziekte
Renaal	met betrekking tot de nieren
Sensitiviteit	de kans dat die test een positieve uitslag geeft bij de mensen die de ziekte hebben
Specificiteit	een maat voor de kans dat bij afwezigheid van de ziekte die de test moet opsporen het resultaat negatief is
Stenose	vernauwing
Subgenuaal	onder de knie
Supragenuaal	boven de knie
Systolische bloeddruk	bovenwaarde van de bloeddruk
Tractus digestivus	het spijsverteringskanaal
Trombus (mv: -i ipv-us)	bloedstolsel
Trombolyse	het oplossen van een trombus met behulp van een antistollingsmiddel
Ulcer (mv: -a)	een zweer, een niet genezende wond
Vasculair	met betrekking tot het vaatstelsel
Vasoconstrictie	het samenknijpen van een bloedvat
Vene	ader

De definities gehanteerd in de bovenstaande verklarende woordenlijst zijn deels afkomstig uit Coëlho, Zakwoordenboek der Geneeskunde, 25ᵉdruk, Elsevier/Koninklijke PBNA, Arnhem 1997.

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Chapter II

Addendum

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De beoordelingscommissie bestaande uit Prof. dr. J.H. van Bockel, Prof. dr. I.H.M. Borel Rinkes, Prof. dr. ir. Y.T. van der Schouw, Dr. F.L.J. Visseren, Emeritus H. van Urk wil ik hartelijk danken voor hun expertise en bereidheid het manuscript kritisch door te lezen.

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Curriculum Vitae

I, Eline Suzanne van Hattum, was born on the 9th of July 1980 in The Hague, the Netherlands. In 1998 I completed my high school education, Gymnasium β, at the Rijnlands Lyceum in Wassenaar. Prior to being admitted to medical school in 1999, I studied pharmacy at the University of Utrecht for one year. During medical school I followed two internships abroad: obstetrics at the J.E. Gonzalez Hospital of Monterrey in Mexico, and dermatology at the Academic Hospital of Paramaribo in Suriname. Furthermore, I joined the student fraternity UVSV/NVVSU where I was given the opportunity to make the eightieth students' year book.

After graduating from medical school in 2006, I joined the department of Vascular Surgery of the University Medical Center Utrecht to work on a PhD project as described in this thesis. During this PhD project, I was supervised by my promoters professor F.L. Moll from the department of Vascular Surgery and professor A. Algra from the department of Clinical Epidemiology at the Julius Center for Health Sciences and Primary Care of the University Medical Center Utrecht. Together we succeeded to obtain a grant from the Lijf en Leven Foundation in Rotterdam. Additionally, at the 4th Congress of the North African and Middle East Chapter of International Union of Angiology in conjunction with 18th Annual Congress of Mediterranean League of Angiology and Vascular Surgery in Cairo, Egypt, I was awarded with the first prize of the open submission oral presentations. Also, I attended several courses in statistics and clinical epidemiology to apply for the degree of clinical epidemiologist B after successfully completing my doctoral program.

Recently, January 2010, I have started my residency in general surgery in the Twee Steden Hospital in Tilburg under the supervision of dr. S.E. Kranendonk. The last two years of my residency are scheduled at the University Medical Center Utrecht under the supervision of professor dr. I.H.M. Borel Rinkes.

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