The use of secondary medical prevention after primary vascular reconstruction: Studies on usage and effectiveness

Annette L. Høgh

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Tutor(s): Jes S. Lindholt, Søren P. Johnsen & Leif P. Jensen,

Official opponents: Eric Wahlberg, Sweden, Gunnar Gislason & Bo Christensen,

Correspondence: Department, Department of Vascular Surgery, Viborg Regional Hospital, Heibergs Allé 4, 8800 Viborg, Denmark

E-mail: Annette.hoegh@m.viborg.dk

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Høgh A, Lindholt JS, Nielsen H, Jensen LP, Johnsen SP. Secondary medical prevention after primary vascular surgery between 1996 and 2006: A shift towards more evidence-based treatment. Eur J Prev Cardiol. 2012 May 25. [epub ahead of print]

Høgh A, Lindholt JS, Nielsen H, Jensen LP, Johnsen SP. Use of Angiotensin-converting-enzyme inhibitors and cardiovascular outcomes following primary vascular reconstruction: A nationwide propensity score matched follow-up study. Accecpted.

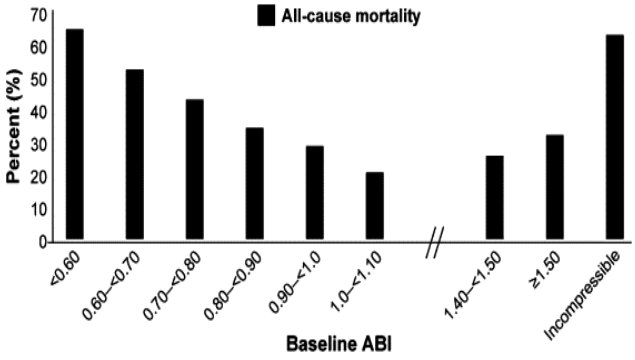
Høgh A, Lindholt JS, Nielsen H, Jensen LP, Johnsen SP. Beta-blocker use an clinical outcomes after primary vascular surgery: A nationwide propensity-matched study.

1. INTRODUCTION

1.1 Introduction to peripheral arterial disease

Peripheral arterial disease (PAD) results from the narrowing of the blood vessels of the lower limbs, predominantly secondary to universal atherosclerotic vascular disease. The generalisation of the disease makes PAD associated with shortened survival due to relationship with other arterial territories, specifically the cerebral and cardiac circulation which leads to a very high risk of fatal and non-fatal coronary and cerebro-vascular events1-5. Symptomatic PAD is associated with a 20-30% greater cumulative 5-years risk of non-fatal myocardial infarction (MI) and stroke3;6. The ankle-brachial pressure index (ABI) is a simple, non-invasive test that is used in clinical practice, as an inexpensive and rapid technique to define PAD, whereby an ABI <0.90 mm Hg suggests the presence of PAD. Moreover, the ABI can be used as an independent marker of increased cardiovascular risk3, as the risk of cardiovascular events and al cause mortality increases as the ABI value decreases7-10 (figure 1.1). In a systematic review, Doobay and Anand reported that the specificity of low ABI values for predicting future cardiovascular outcomes was high (87.9%) and that the sensitivity was low (41%), although the sensitivity was shown to increase to 85% in high risk populations11.

Figure 1
All cause mortality as a function of baseline ABI(TASCII fig A1) 12



Conventionally, PAD is categorised into four clinical stages using the Fontaine classification (figure 1.2). In general, for every patient with symptomatic PAD, there are another three to four patients with asymptomatic PAD. Approximately one-quarter of the patients with intermittent claudication will progress to a higher Fontaine stage over time; these patients may require vascular surgical reconstruction to prevent functional decline, mobility loss, and future major amputation due to rest pain or tissue loss. Asymptomatic PAD patients have nearly the same increased risk of experiencing cardiovascular events as symptomatic PAD patients13;14. In general, patients assigned Fontaine stages of II-IV are observed in the health

care system and these patients are constituted the focus group of this thesis.
In addition to preventing leg amputation and relieving PAD symptoms, the aim of PAD treatment is to reduce the risk of future cardiovascular events by secondary medical prevention. Current national and international guidelines recommend that lipid lowering drug and anti platelet therapy for all PAD patients, both symptomatic and asymptomatic, supplemented with aggressive blood pressure lowering treatment, independent of patients age or gender12;16-19.

Table 1
Fontaine classification of the severity of PAD15

	Fontaine stage	Description
I	Asymptomatic	PAD present but no symptoms
II	Intermittent claudication	Cramping pain in leg muscles precipitated by walking and rapidly relived by rest
III	Rest pain	Constant pain in feet (often worse in night)
IV	Tissue loss	Ischemic ulceration or gangrene

1.2 Epidemiology of peripheral arterial disease
Findings from epidemiological studies, which used ABI to identify PAD patients, suggest that the prevalence proportion of PAD is approximately 3 to 10 % in the general population. Moreover, the prevalence of PAD increases with age as the prevalence proportion increases to 15 to 20% in individuals of both genders and over the age 70 years13;14;20-22. The proportion of the population > 60 years old continues to grow, and women constitute the majority of this aging population. In 1970, 17.5% of the Danish population was > 60 years old, whereas this proportion was 22.7% in 2009. Gender specific mean life expectancy has increased from 72.2 in 1990 to 76.5 in 2009 for men and from 77.8 in 1990 to 80.7 in 2009 for women23.
However, the association between gender and the appearance of symptomatic PAD is less clear. The Framingham Heart Study found that men have nearly twice the risk of developing intermittent claudication as women24, whereas other studies have not found statistically significant differences14. In addition certain studies have detected a predominance of women placed at the symptom scale´s outer boundaries, and the majority of these patients was asymptomatic or presented with critical limb ischaemia25-27. Historically, women have had higher amputation rates and have been less likely to undergo arterial reconstruction as a fist-line procedure when compared with men28.

1.3 Cardiovascular risk factors
The management of PAD patient must to be planned in the context of modifiable systemic risk factors for atherosclerosis, as well as the prevention of major amputations. Numerous cardiovascular risk factors are associated with atherosclerotic disease progression29, and these risk factors can be divided into the following three major groups:

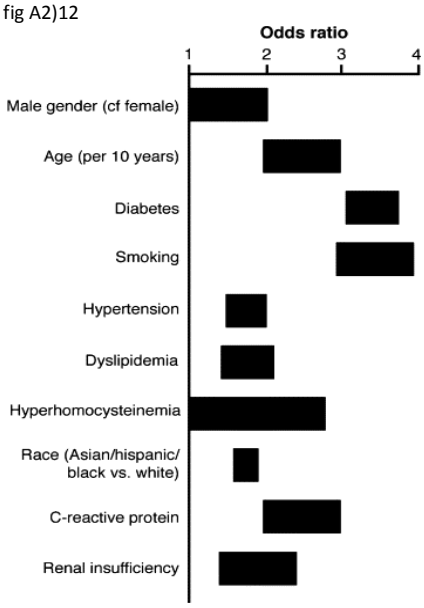
1. Existing disease factors, such as diabetes, MI, stroke and PAD
2. Non-modifiable factors, such as age, gender and genetics
3. Modifiable factors, including smoking, obesity, hypertension, serum lipids and the control of diabetes

The objective of secondary medical prevention is to reduce the risk of vascular morbidity and mortality. With the advantage of this treatment strategy, the development of atherosclerosis can be attacked on numerous fronts simultaneously to decreased vascular inflammation, stabilising atherosclerotic plaques, decreasing endothelial dysfunction and prevent thrombosis. In this thesis, we will focus on blood pressure lowering treatment, lipid lowering drugs and anti platelets agents.

1.4 Secondary medical prevention

1.4.1 Blood pressure lowering drugs
Systemic blood pressure control in PAD patients is challenging due to the percent of calcified arteries without elasticity as a result of atherosclerosis. However, effective blood pressure lowering treatment can decelerate the progression of PAD, as well as reduce the overall risk of MI, stroke and cardiovascular death in PAD patients with or without hypertension 5;30-33. According to a meta-analysis of 147 randomised studies, the reduced risk of cardiovascular events in patients with uncomplicated hypertension (treated with blood pressure lowering drugs) are mediated solely by reduction in blood pressure, irrespective of the blood

Figure 2
Approximate range of odds ratios for risk factors associated with PAD (TASCII fig A2)12

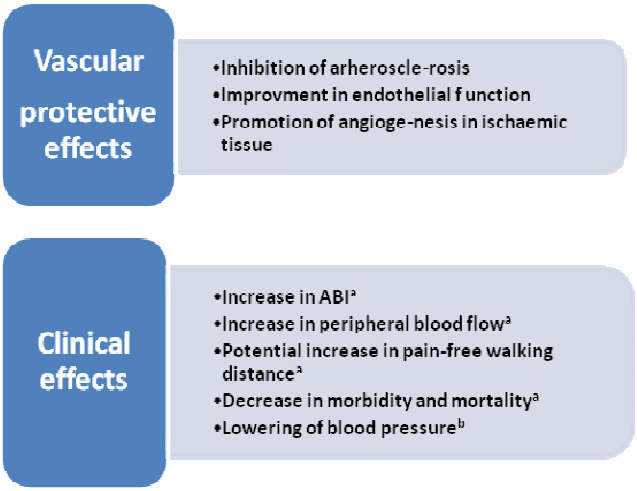


pressure lowering drug selected34. This is consequently no general consensus on first choice drug for un-complicated antihypertensive treatment (lack of level A evidence)35. Thus, the therapeutic goal is to attain a blood pressure of 130/80 mmHg, according to the recommendations of the European Society of Hypertension. In this study, the principal focus will be on angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists (ACE/ATII) and beta blockers, which are the only blood-pressure lowering drugs to demonstrate specific results regarding the cardiovascular events experienced by PAD patients36;37.

1.4.2 Angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists
Previous, randomised controlled clinical trials, including those studying symptomatic and asymptomatic PAD patients with co-existing

cardiovascular disease, showed that ACE inhibitor use was associated with a reduced rate of al cause mortality, MI, stroke and revascularisation37;38. ACE inhibitor treatment was also shown to be cost-effective with regards to cardiovascular risk reduction in asymptomatic PAD patients39. These trials indicated that ACE inhibitor should be the first-line treatment for symptomatic and symptomatic PAD patients with or without hypertension, as these drugs presumable have effects beyond their blood pressure lowering effects on cardiovascular mortality and morbidity40, such as lengthened duration of pain-free walking time41-43. The causality, responsible for these results is unknown but may be related to a combination of advantageous changes in the peripheral circulation, cardiac function, muscle metabolism, and endothelial function42;44-46. With regards to endothelial function, ACE inhibitors seem to have beneficial effects, as these drugs affect the collagen/elastin ratio in the major arteries, to decrease vascular stiffness and contribute to modeling of the artery walls (anti-proliferation and anti-immigration effects)46.

Figure 3
Vascular-protective effects of angiotensin-converting enzyme inhibitors (adapted from Hirsch et al. 2003)47



a Demonstrated in small-scaled clinical investigations
b Demonstrated in large-scaled prospective investigations

Furthermore, two small case-control studies concluded, that prior ACE/ATII use is associated with lower troponin release in non-ST-elevation acute coronary syndrome as well as and beneficial effects related to vascular reactivity and the coagulation system48;49. However, the hypothesis concerning the beneficial effects of ACE inhibitors beyond their blood pressure lowering effects, has been questioned38;50. Therefore, the ACC/AHA guidelines recommend ACE inhibitor treatment in symptomatic PAD patients as a class II, level A recommendation17.

1.4.3 Beta blockers
Traditionally beta blockers has been the first choice for secondary medical prevention following MI or chronic angina for cardioprotection34;51. However, their use remains controversial and is has not been recommended for PAD patients due to suspected adverse effects, including α-receptor mediated peripheral vasoconstriction and deterioration of the peripheral circulation, which could lead to worsening of intermittent claudication symptoms. However, two meta-analysis disproved this hypothesis, and concluded that beta blockers were safe for PAD patients, as they did not affect the patients' walking capacity or symptoms of intermittent claudication52;53. Still, other contraindications could be taken in to account, including asthma, chronic obstructive pulmonary disease and atrioventricular (AV) block31;52. The rate of occurrence of adverse effects leading to cessation of the initiated beta blocker treatment was 12% in a population of patients with prior MI and symptomatic PAD54.
Beta blockers have also been reported to cause undesirable changes in cholesterol metabolism55-59, related to decreased HDL and increased triglyceride-concentrations. The long-term impacts of these treatment effects remains unknown and the use of beta blockers could theoretically increase the progression of PAD symptoms due to impairments in arterial occlusion. However, beta blockers could also theoretically prevent disruption of atherosclerotic vulnerable plaques by reducing heart rate and blood pressure, which could delay the patho-physiological mechanisms underlying acute coronary syndrom21

1.4.4 Alternative anti-hypertensive agents
Large controlled trials addressing the effects of calcium antagonists and diuretics in PAD patients are lacking. Nevertheless, there is little doubt that diuretics and calcium antagonists have been shown to be effective anti-hypertensive agents both for lowering blood pressure and for reducing cardiovascular morbidity and mortality in patients with uncomplicated hypertension31;34;60.

1.4.5 Lipid lowering drugs
The association between the levels of circulating cholesterol and cardiovascular morbidity and mortality is well established in high-risk individuals, as well as PAD patients61;62. The POCH study, which was followed by a Cochrane review in 2000, stated that all PAD patients should be receipted lipid-lowering drugs independent of their baseline cholesterol levels63;64. The rational for this recommendation is based on the dual effects of lipid-lowering treatment, whereby endothelial function improves and the serum cholesterol level decreases (through the inhibition of hydroxymethylglutaryl-CoA reductase, representing the rate-limiting step in the mevalonate pathway for cholesterol synthesis in the liver). These effects results in a decreased subsequent risk for MI, stroke, and vascular death. Furthermore, use of statin is associated with functional improvement in PAD patients as demonstrated by improved walking distances following tratment65;66, and also to have anti-inflammatory properties67. Current guidelines recommend the therapeutic goal of reducing total serum cholesterol concentrations to less than 4.5 mmol/l and low den-sity lipoprotein cholesterol concentration to less than 2.5mmol/l.

1.4.6 Anti platelets therapy
Numerous large, randomised trials have shown that anti platelet therapy reduces the risk of both fatal and no-fatal cardiovascular events, in high-risk patients, including symptomatic PAD patients68;69. However, no studies have demonstrated a delay or reduction in the progression of lower limb athero-thrombotic lesions in PAD patients using anti platelets therapy.
PAD patients exist in a pro-thrombotic state with increased platelet activation, also after vascular reconstruction, causing major concern due to the risk of vascular-graft occlusion70;71. Currently, there is no evidence supporting an additive effect of dipyridamole in combination with aspirin in patients with PAD, as observed in patients with stroke71. However, additive effects were observed in the CHAISMA-study following the combined administration of aspirin

and clopidogrel to symptomatic PAD patients72.

1.5 Usage and effectiveness of secondary medical prevention

1.5.1 Usage

Although there is strong evidence for the biological rationale and often also the efficacy of secondary medical prevention in patients with PAD undergoing primary vascular reconstruction, including lipid lowering therapy and anti platelet therapy supplemented with aggressive blood pressure lowering treatment, several studies have indicated that the use of secondary medical prevention generally is insufficient for patients with PAD25;35;73-78 (see table 2). Paradoxically, several studies indicate that PAD patients in general are less likely to receive optimal secondary medical prevention and intensive risk factor modification than patients with coronary artery disease or former stroke76;79-83. These observations were found to be particularly valid for the elderly and women25;84;85. The prescription rate is also expected to be influenced by both system- and patient-related factors including socio-demographic and clinical factors.

No previous studies have, to our knowledge, explored the possible existence and size of age-related differences in the use of secondary medical prevention after primary vascular reconstruction. However, age-related differences in the use of secondary medical prevention have previously been found among patients with ischemic stroke86 or acute coronary syndrome87, which indicate that age-related differences in the use of secondary medical prevention are a widespread phenomenon among patients with cardiovascular disease. Gender-related differences in the use of secondary medical prevention have previously been reported among PAD patients25;73. In the Swedish study men showed a higher chance of receiving e.g. lipid-lowering therapy (adjusted odds ratio = 1.3) and anti-platelet therapy (adjusted odds ratio = 1.6) compared to women. Recently, substantial geographic international and national variations in the use of secondary medical prevention have been reported, and this variation reflects the problem of treatment implementation25;88;89. The current clinical guidelines uniformly recommend secondary medical prevention in patients with PAD, and major efforts are done across health care systems in order to ensure the implementation of these recommendations. However, little is known about the effects of these efforts, as there are only limited up to date population-based data available on the use of secondary medical prevention among unselected symptomatic PAD patients. See the appendix for a review of the discussed studies related to the use of secundary medical prevention.

1.5.2 Efficacy and effectiveness

The efficacy of a treatment describes the results of the intervention in an `ideal situation´ where the patients often are highly selected and the intervention is closely monitored; leading to a high internal validity. A typical set up for characterizing efficacy is a randomized controlled trail, where the patients have accepted the intervention and are highly motivated to follow the study instructions. In contrast, the effectiveness of a treatment describes the result of the intervention in a real-life situation. The results from effectiveness studies have high external validity, but may be influenced by patient compliances or extraneous effects from other diseases than the main target of the investigation91.

Currently, the efficacy of blood pressure lowering treatment among PAD patients have only been examined concerning ACE inhibitors33;38 and beta blockers33;53; the studies found both treatments associated with symptom relief or reduction in cardiovascular events among PAD patients. The effectiveness of ACE inhibitor treatment (as well as other secondary medical prevention) has solely been described by Feringa et al92, who showed ACE inhibitor use to be associated with a reduction in long-term mortality, among PAD patients92. The blood pressure lowering treatment is a key component in the secondary medical prevention regarding PAD patients. However data on the efficacy and particularly the effectiveness of different classes of anti hypertensive treatment few and less clear. See the appendix for an overview of the discussed studies related to the efficacy and the effectiveness of ACE inhibitor and beta blocker use among PAD patients.

2. AIMS

Study I: To determine whether age- or gender related differences exist in the use of secondary medical prevention following primary vascular reconstruction in four pre-defined time periods (½, 3, 5, and 10 years).

Study II: To determine whether there is time- or geography related differences exist in the use of secondary medical prevention following primary vascular reconstruction, from an early period (1996 to 2000) compared with a later period (2001 to 2006).

Study III: To examine the associations between the use of ACE/ATII and the clinical outcomes (all cause mortality, MI, stroke, major amputation and/or recurrent vascular surgery), of patients undergoing primary vascular reconstruction.

Study IV: To examine the associations between the use of beta blocker and the clinical outcomes (all cause mortality, MI, stroke, major amputation and/or recurrent vascular surgery), of patients undergoing primary vascular reconstruction.

3. MATERIALS AND METHODS

3.1. Data sources

3.1.1 The Danish Vascular Registry

The Danish Vascular Registry is a national clinical registry containing prospective information on all vascular procedures performed in Denmark since 1996. The primary objective of this registry are surveillance and quality improvement, and the registry contains data on 65 variables (including indication for surgery, timing of surgery (acute/elective), patient characteristics, type of intervention, patency at discharge, discharge destination, and post-operative complications)93. Reporting is mandatory for all vascular surgery departments (n=9) and the registry covers 99.2% of all vascular procedures performed at Danish hospitals (www.karbase.dk, 2009 annual report). The accuracy of the Danish Vascular Registry was previously described as good93, and our investigation confirmed this assessment. To assess the validity of the data in the registry, we compared information recorded in the registry to information recorded in the medical records of 200 randomly selected patients. We found discrepancies of < 1% for most variables, including patency at discharge and discrepancies of < 3% related to the type of surgery.

3.1.2 The civil Registration System

Each Danish citizen receives a unique civil 10-digit civil identification number at birth. This number encodes the individual´s gender, date of birth, change of address, date of emigration, and information on vital status since 196894;95. The personal identification number

enables unambiguous individual linkage between population-based administrative and health care registries.

3.1.3 The Danish National Patient Registry
The Danish National Patient Registry retains information on all discharges from somatic hospitals since 1977. These files include information regarding the date of discharge for up to 20 discharge diagnoses and procedures, and are coded according to the International Classification of Diseases (8th revision until 1993 and the 10th revision thereafter)96. Contacts with outpatient clinics and emergency departments have also been recorded since 1995. The use of the Danish National Patient Registry enabled the construction of a complete hospitalisation history for each patient. The predictive value of diagnoses registered in the Danish National Patient Registry have previously shown to be high for a range of important conditions, including myocardial infarction, cancer, and diabetes97;98. Our study confirmed this assessment, as we found good concordance (no mismatches concerning operations-dates and codes, information on former vascular surgery, or patency at discharge) in a comparison of the data from our study population to those from the Danish Vascular Registry and the the Danish National Patient Registry. Nevertheless 2.7% of the patients appeared in the Danish Vascular Registry, but not in the Danish Patient Registry.

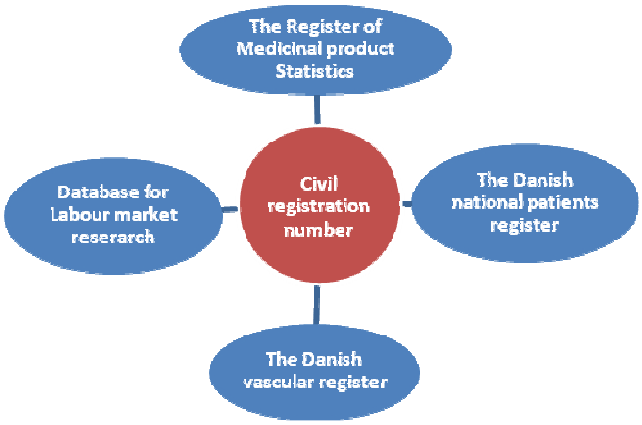
3.1.4 The Integrated Database for Labor Market Research
The Integrated Database for Labor Market Research, which was established in 1980, retains yearly updated information on socioeconomic status for the entire Danish population. The registry contains information on gross income, education level, employment status and marital status as well as more than 250 other variables. The database is maintained by Statistics Denmark.

3.1.5 The Register of Medicinal Product Statistics
This register contains data from 1995 on regarding for all prescription drugs dispensed at all Danish pharmacies, including the type of drug according to the Anatomical Therapeutically Chemical (ATC) classification system99, and the date it was dispensed. With the exception of low-dose aspirin, all types of cardiovascular drugs in Denmark are available by prescription only. However, aspirin is available by prescription to patients with chronic diseases and to pensioners, and they are reimbursed the cost.

3.1.6 Statistics Denmark
Statistics Denmark is a governmental institution within the Ministry of Economics and Business Affairs. It maintains its own registries, as well as data from other public registries, and this system can be used to crosslink and assemble data into specific datasets, according to personal civil registration number (see figure 4).

3.2 Study population
All studies were conducted within the entire Danish population (n≈5.5 million) on the basis on a tax-supported health care system provided by the Danish National Health Service. The system allows free access to hospital care, general practitioners, and provides partial reimbursement for expenses related to a wide range of prescription drugs.
The study population was identified in the Danish Vascular Registry (see section 4.1.1) and included all Danish patients with PAD who underwent primary vascular surgical or endovascular reconstruction, in between 1996 and 2007. The included regions of vascular reconstruction consisted of the abdominal arteries (aorta-iliac), groin arteries (including femoral and popliteal arteries), and crural arteries. Patients with unknown surgical codes were excluded. The patients underwent surgery due to moderate intermittent claudication, ischaemic rest pain, ulceration or gangrene. The patients were included based only on their first procedure during the study period. We also excluded patients who died within 30 days after discharges and patients younger than 40 years of age.
Information on patient vital status during follow-up was obtained through linkage with the `Civil Registration System´. Furthermore, patients were included only if they had a valid civil registration number that enabled unambiguous linkage between public registers, and if they resided in Denmark, and therefore available for follow-up.

Figure 4
Linkage of nationwide registers



3.4 Study designs

3.4.1 Studies I and II
Study I and II were constructed as nationwide, population-based studies using available, detailed and complete follow-up information on an individual-level. In study I, prescribed medications were assessed at 6 months (n=16,945), and 3 (n=9,520), 5 (5,895), and 10 years (n=1,072) after primary vascular reconstruction. Furthermore, study I used early and late calendar period from 1997 to 2000 and 2001 to 2006 as pre defined time points, respectively. Study II also used early and late calendar periods as pre-defined time points, and in addition, patients without at least six months of follow–up were excluded (n=16,945). The year 2000 was used as the cut-off point because the first international guidelines for the management of PAD were published during this year100.
Application of secondary medical prevention was defined as at least one prescription filled within 90 days before or after each predefined time point.

3.4.2 Studies III and IV
Studies III and IV were cohort studies, comparing the clinical outcome among users of secondary medical prevention to non users. The clinical outcomes were defined as all cause mortality, MI, stroke, major leg amputation or the need for supplemental vascular surgical reconstruction. The included study period was from 1996 to 2007. ACT/ATII and beta blocker users were defined as those individuals who filled at least one prescription within 180 days of receiving primary vascular reconstruction. Propensity score matching101;102 was used to reduce the risk of confounding; matching

users with non users. The matching was followed by a Cox regression analysis using a multi-variable model based on a competing risk analysis of the clinical out-comes.

3.5 Exposure

We identified all prescriptions administrated to the included patients up to 10 years after primary vascular reconstruction, and our primary focus was on cardiovascular secondary medical prevention. The prescriptions were classified according to their Anatomical Therapeutic Classification (ATC) codes.

We created a category of combination therapy to include patients who were prescribed any lipid-lowering drug plus any anti-platelet therapy plus any blood pressure lowering treatment. Prescription rates of anti platelets drugs were treated as a single prescription (aspirin, dipyridamole and/or clopidogrel), we did not take combinations of anti platelets drugs into account. Information on all studied secondary medical prevention was collected prior to hospitalisation for primary vascular reconstruction, as well as during the entire follow-up period. Concerning studies I and II, the data were collected +/- 90 days around the pre-defined points in time, as prescriptions for secondary medical prevention are generally issued for three months at a time in Denmark. In studies III and IV prolonged use of secondary medical prevention after discharge was included as time dependent variables, in order to account for breaks and/or cessation of treatment.

Figure 3
Anatomical Therapeutic Classification (ATC) code

Medication	ACT codes
ACE/ATII	C09
Beta-blockers	C07
Calcium antagonists	C08
Diuretics	C03
Anti platelet drugs	B01
Lipid-lowering drugs	C10

3.6 Covariates

A numbers of factors may have affected the use of secondary medical prevention among PAD patients undergoing primary vascular surgery. In order to account for these factors, in the studies included in this thesis, we matched and/or adjusted for a wide range of potential confounding factors (comorbidity, socioeconomic status, indications for primary vascular reconstruction, surgery region, vascular patency at discharge, discharges destination and smoking habits).

3.6.1 Comorbidity

To adjust for confounding factors by comorbidity, we constructed hospitalisation histories for all included patients dating back to 1977. According to the discharge diagnoses from the Danish National Patient Registry, we computed the comorbidity index score (at the time of surgery), as desribed by Charlson et al 103. The Charlson comorbidity index covers 19 major disease categories (including MI, heart failure, cerebro-vascular diseases, diabetes, and cancer) weighted according to their prognostic impact on patients' survival. This index has previously been adapted but also validated regarding the use of hospital discharge registry data 98;104. We calculated these scores based on previous discharge diagnosis recorded prior to the date of hospitalisation, and the following three categories were related according to the degree of comorbidities: `Non´ (score 0), `low comorbidity´ (score 1-2), and `high comorbidity´ (score >2). In studies III and IV we preformed supplemental analysis by stratification, according to the increased risk of MI and stroke, which are both diseases with well-established prognostic value for future clinical outcomes in symptomatic PAD patients.

3.6.2 Socio-economic variables

The Integrated Database for Labor Market Research was used to identify socio-economic data.

We classified patients according to employment (employed, pensioner, or other), marital status (single, married, widow, divorced), gross income (in quartiles), and education level (primary or lower secondary school, upper secondary school or vocational education, and higher education).

3.6.3 Information on vascular surgery

The Danish Vascular Registry provided information on the following variables: Acute/elective surgery, region of surgery (central arteries (aorta-iliac), groin arteries (including femoral and popliteal arteries), or crural arteries), vascular patency at discharge (open or closed), discharge destination (home, hospital, nursing home, no information or death) and smoking habits at the time of primary vascular reconstruction (current smoker, former smoker, non smoker or no information).

3.7 Statistical analysis

All of the analyses were performed using Stata-softwear (StataCorp LP, College Station, TX, USA) version 11.0 and SAS 9.2 (Rx64 2.13.0). The statistical significance level was set to 0.05 for all analyses.

3.7.1 Studies I and II

All of the data were categorised and are presented herein as percentage frequencies. The equality between proportions was also tested (two-sided test of proportions Chi2 test).Thereafter, a generalised linear model, according to the Poisson distribution in a log-linear model with robust error estimates, was used to perform crude and adjusted comparisons between the groups examined and provide relative risk estimates (RR). In study I the analysis was preformed across age and gender groups using men between 40 to 60 years of age as reference. In study II, the analysis was preformed across the two calendar periods (early (1997 to 2000) and late period (2001 to 2006)) and geographic variations with the early period and the capital area as references, receptively.

We used Poisson regression rather than a logistic regression because of the high prevalence of drug use and the need to adjust for a range of covariates, which may have caused convergence problems in a log-binomial model105;106.

For the adjusted analyses, we included the following variables at the time of primary vascular reconstruction: Comorbidity index score, socioeconomic status (gross income, education level, marital status and employment), timing of surgery (acute/elective), discharge destination, region of surgery (abdominal arteries (aorto-iliac), groin arteries (including femoral and popliteal arteries) and crural arteries), vascular patency at discharge and smoking habits. In study I, the numbers of patients older than 80 years of age with available 10-year follow-up data was too small to perform meaningful comparisons, and thus, these patients were excluded from the multivariable analyses.

Figure 4.1 Study III (ACE/ATII): Standardised differences in variables included in the propensity score for the entire study population (○) and for the propensity score-matched patients (●)

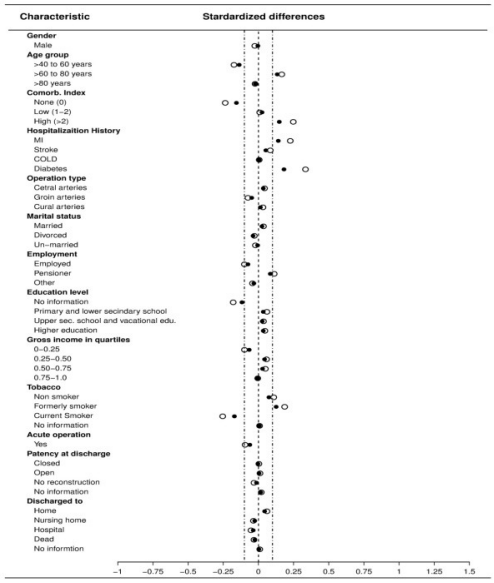


Figure 5.2 Study III (ACE/ATII): Variance ratios of variables, including the propensity score for the entire study population (○) and for the propensity score-matched patients (●)

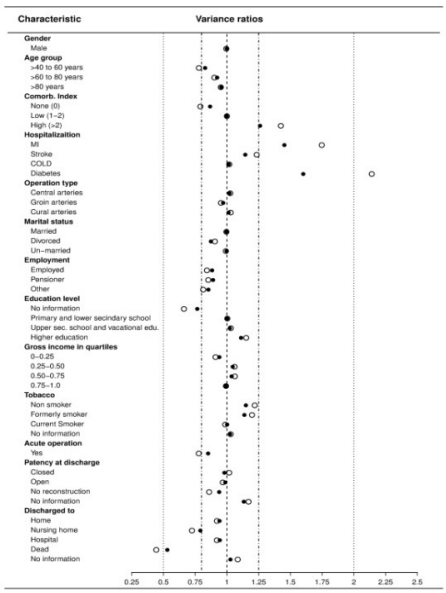


Figure 5.3 Study IV (Beta blockers): Standardised differences in variables included in the propensity score for the entire study population(○) and for the propensity score-matched patients (●)

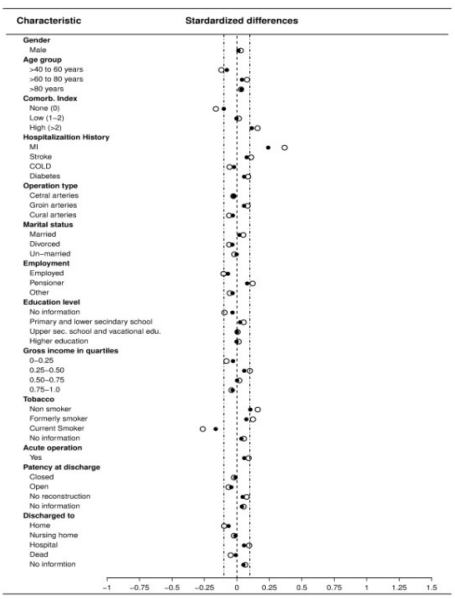
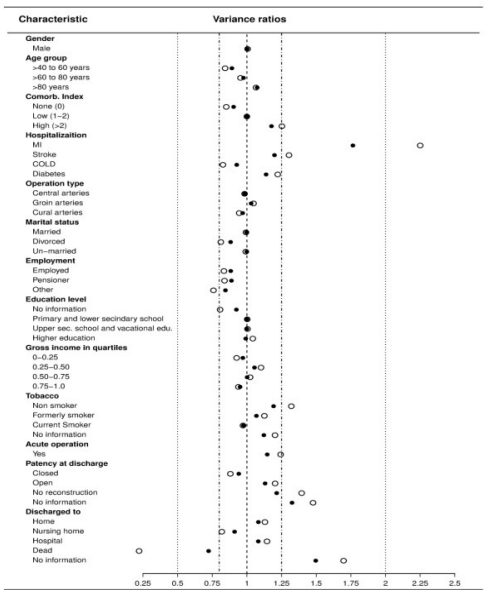


Figure 5.4 Study IV (Beta blocker): Variance ratios of variables, including the propensity score for the entire study population (○) and for the propensity score-matched patients (●)



3.7.2 Studies III and IV

The characteristics of the patients were compared using a two-sample test of proportions. ACE/ATII- and beta blocker users were defined as those individuals who filled at least one prescription within 180 days after receiving after primary vascular reconstruction and were matched with non users such that as many as five non users could be matched with each ACE/ATII- or beta blocker user. ACE/ATII- or beta blocker users without a matching non user were excluded from the analysis (see flow diagrams 3.3.3 and 3.3.4). Because ACE/ATII- and beta blocker use was not randomly assigned in the study population, we used propensity score matching (caliper method with 0.2 standard deviation of the logit of the estimated propensity score) to overcome or at least reduce the risk of bias due to confounding factors102;107. The following covariates were matched: Gender, age-group, comorbidity index, prior hospitalisation with MI, stroke or diabetes, operation type, marital status, employment, education level, gross income (in quartiles), smoking, acute operation, patency at discharge, discharge destination and pre-surgery drug use (ACE/ATII, beta- blockers, calcium antagonists, diuretics, anti-platelet drugs and lipid-lowering drugs). An absolute standardised difference of <10% and a variance ratio between 0.8 and 1.25 were considered to support the assumption of balance between groups101;108 as shown in figures below (○ for the entire study population and ● for the propensity score-matched patients). On Average, all of the variables achieved full balance after matching (● was placed between the dotted lines to represent the accepted variation mentioned above). However, balance after matching was not achieved for previous hospitalisation due to MI and diabetes in study III (ACE/ATII use) and MI in study IV (beta blocker use), respectively. This matching was followed by a Cox regression analysis (by estimating adjusted hazard ratios (Adj. HR)) which enable adjustment to be made for potential residual confounding factors using non users as the reference point.

The Cox regression analyses used a multi-variable model that was based on the competing risk analysis of the end points (all cause mortality, MI, stroke, major amputation and/or recurrent vascular surgery) and adjustment were made for baseline covariates as well as for drugs used during the follow- up period (angiotensin II receptor antagonists, angiotensin-converting-enzyme inhibitors, calcium antagonists, diuretics, anti-platelet drugs and lipid-lowering drugs). We evaluated the robustness of the study findings by repeating the analyses after stratifying for previous MI and diabetes, as full balance between ACE/ATII or beta blocker users and non users was not achieved for these two characteristics despite propensity score matching. Furthermore, we repeated the analysis using the entire study population and included the propensity score for the use of ACE/ATII or beta blockers as a covariant, whereby the data were first transformed it into cubic splines (a continuous, smooth function that provides a generally fair and robust approach for adapting linear methods to non-linear relationships).

3.8 Permissions

According to Danish law, projects based on public nation-wide registers do not require the consent of the patients studied. Permission to use and link data from public registers was obtained from the Danish Data Protection Agency and Statistics Denmark.

4. RESULTS

The main results of the four studies are summarized below.

Figure 6 illustrates the proportions of filled prescriptions for secondary medical prevention among patients who underwent secondary medical prevention was moderate to low, although an upwards trend was observed during the observation period. Major changes in the use of lipid-lowering drugs (33.7% in 1996 77.4% in 2006; adjusted RR 1.95, 95% CI 1.81-2.10) and diuretics (74.4% in 1996 vs. 49.9% in 2006; adjusted RR 0.68, 95% CI .64-0.71) were observed over time. The overall administration of blood pressure lowering treatments did not change, although the type of treatment shifted from the use of diuretics and calcium antagonists to an increased use of ACE inhibitors and ATIIs. The use of combination therapy (concomitant lipid-lowering, anti platelet, and any antihypertensive therapy) increased from 29.1% in 1996 to 67.6% in 2006 (adjusted RR 1.95, 95% CI 1.80-2.12).

4.1 Results of study I

Among the 20761 included patients 63% were 61 to ≤ 80 years of age at the time of primary vascular reconstruction. We observed the highest levels of co-morbidity, as well as a lower proportion of abdominal reconstruction among patients >80 years of age. The descriptive characteristics stratified, by age and gender is displayed in table 3.

All of the examined drugs underwent a general decline (in the range of 10-30%) in usage between 6 months and 3 year after primary vascular reconstruction, after which point the use of these drugs stabilised. However, after 10 years the use of lipid lowering drugs and anti platelet drugs returned to the level observed 6 months after surgery.

Figure 7 shows the proportions of patients who filled prescriptions for secondary medical prevention at 6 months and 3, 5 and 10 years after primary vascular reconstruction according to gender and age. The corresponding adjusted relative risks with the 95 % confidence intervals (RR 95, % CI) are displayed in table 4.

The observed gender and age related differences shown in figure 7 were not significant after adjustments were made for co-morbidity and socio-economic and clinical factors (Charlton's co-morbidity index, gross income, education level, marital status and employment, smoking, acute/non-acute surgery, discharge destination and patency at discharges) related to the first 6 months after primary vascular reconstruction. However, age-related differences in the use of combination therapy persisted 3 and 5 years after surgery, men and women who were > 80 years of age demonstrated adjusted RRs (for receiving combination therapy) of 0.63 (95% CI: 0.39-1.02) and 0.48 (95% CI: 0.31-0.75) 3 and 5 years after surgery, respectively, compared with men who were 40 to ≤ 60 years of age. In addition, more women than men were found to receive secondary medical prevention, although many of the observed gender-related differences did not reach statistical significance. In addition, more women than men were found to receive secondary medical prevention, although many of the observed gender-related differences did not reach statistical significance.

We stratified the analyses according to early (1996 to 2000) and late (2001 to 2006) periods, and focused on prescriptions that had been filled 6 months after surgery. The results indicated striking differences regarding the users of secondary medical prevention (see table 4), and these age-related differences for all drugs were either completely eliminated or substantially reduced in size during the late period.

Figure 6
Proportions of Danish patients with symptomatic PAD who filled specific prescriptions for secondary medical prevention between 1996 and 2006

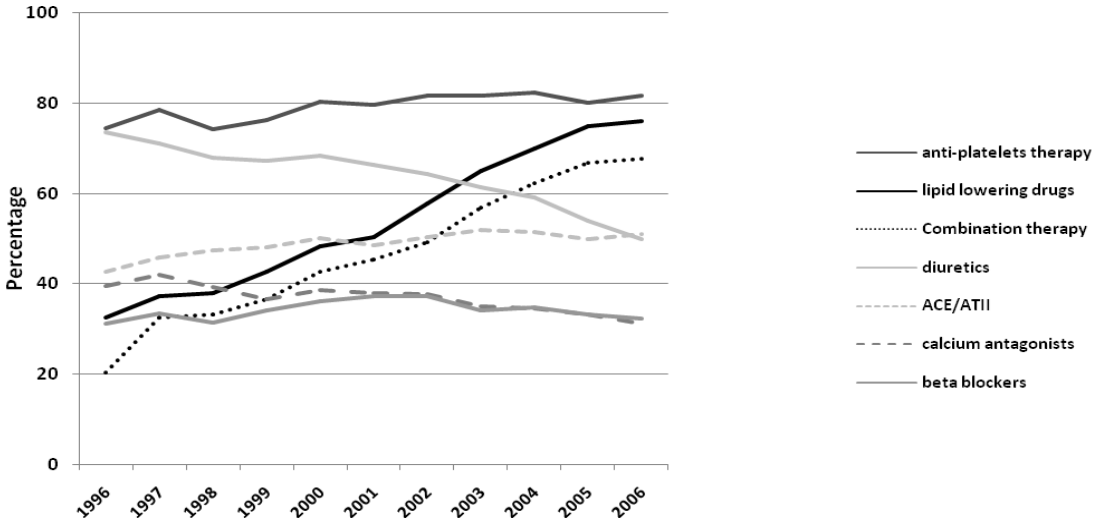


Figure 5 Percentages of patients who filled prescriptions for secondary medical prevention 6 months and 3, 5 and 10 years after primary vascular reconstruction. A. ACE/ATII, B. Beta blockers, C. Calcium antagonists, D. Diuretics, E. Anti platelets therapy, F. Lipid lowering drugs, G. Combination therapy: Lipid lowering drugs, anti platelets therapy and any anti hypertensive therapy

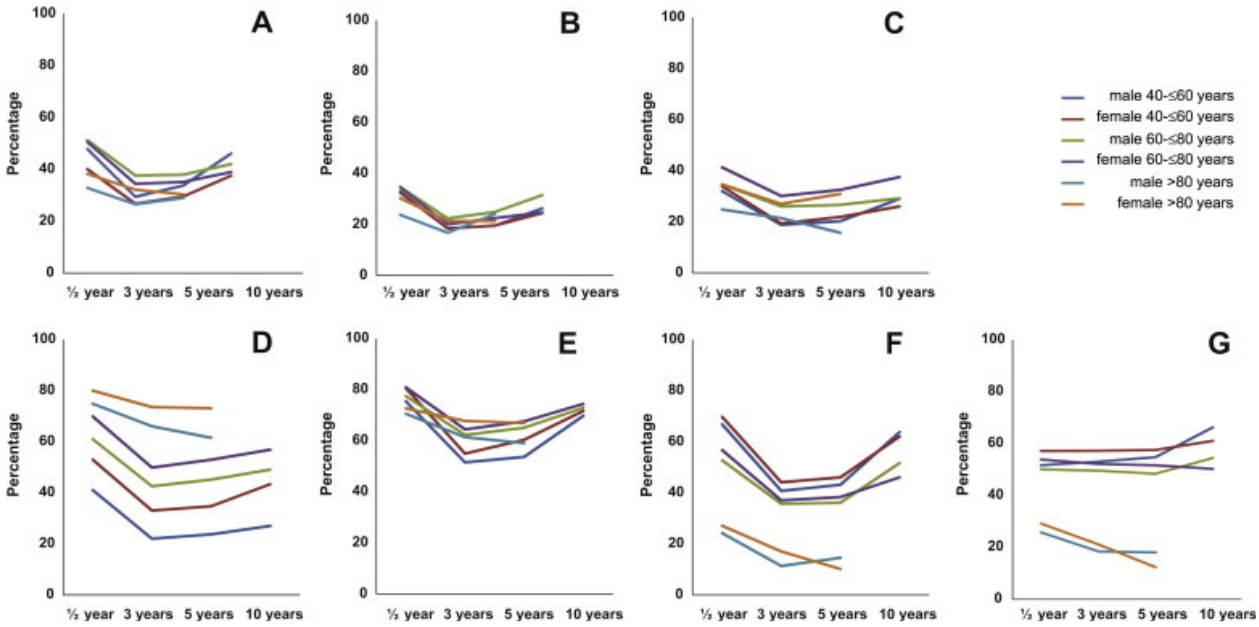


Table 3 Descriptive characteristics, stratified by gender and age; study I

Age / Gender	Female 40-60 years N=1906 (9.2%)	Male 40-≤60 years N=3219 (15.5%)	Female 60-≤80 years N=5930 (28.6%)	Male 40-≤60 years N=7081 (34.1%)	Female 60≤80 years N=1586 (7.6%)	Male >80 years N=1057 (5.1%)
Comorb. Index						
None (0)	39.5	38.5	30.1	25.8	30.1	25.6
Low (1-2)	47.5	46.8	51.6	51.3	47.4	50.2
High (>2)	13.1	14.8	18.3	22.9	22.4	24.1
Hospitalisation history						
MI	4.6	8.7	8.0	14.5	8.9	13.4
Stroke	6.2	7.0	10.0	12.7	14.0	14.2
COLD	5.9	3.6	9.2	9.2	8.0	9.6
Diabetes	10,3	10.6	12.4	14.0	16.3	13.3
Operation type						
Abdominal arteries	66.0	51.9	45.8	39.9	19.7	26.1
Groin arteries	20.2	23.6	28.0	28.5	42.7	33.1
Crural arteries	13.9	24.3	26.2	32.1	37.6	40.8
Socioeconomic status						
Marital status						
Married	62.6	57.8	42.1	64.6	14.7	52.2
Widow	7.6	2.8	39.2	14.8	73.2	39.0
Divorced	21.9	23.6	14.5	14.7	6.6	5.4
Never married	7.8	15.8	4.3	6.0	5.6	3.4
Employment						
Employed	49.8	61.5	3.1	8.8	0.2	1.0
Pensioner	58.4	27.6	95.5	89.4	99.8	99.0
Other	11.9	10.9	1.4	1.8	0	0
Education level						
No information	0.1	2.0	6.9	6.0	68.3	61.9
Primary and lower secondary school	59.2	9.6	65.2	45.2	23.9	18.7
Upper sec. school and vocational edu.	32.8	48.2	21.5	38.2	5.4	13.9
Higher education	7.3	10.1	6.9	10.6	2.4	6.0
Tobacco						
Non smoker	7.4	6.7	17.4	12,4	49,3	26.4
Formerly smoker	22.8	21.8	28.3	32.1	22.3	32.5
Current smoker	63.6	66.5	48,0	50.1	19.8	32.8
No information	6.2	5.3	6,3	5.3	8.7	8.2
Patency at discharges						
Closed	3.0	3.0	3.2	2.7	3.6	3.0
Open	91.6	91.1	91.5	92.5	89.2	92.6
No reconstruction	4.4	4.7	3.5	3.5	5.8	4.9
No information	1.1	1.3	1.8	1.3	1.5	0.9
Discharged to						
Home	84.2	84.4	79.1	78.4	60.7	63.5
Nursing home	0.2	0.3	1.0	0.7	5.7	4.9
Hospital	14.6	14.0	18.2	19.3	23.1	30.6
Death	0.1	0.2	0.3	0.1	0.1	0.4
No information	0.9	1.2	1.5	1.1	1.4	0.7

Table 4 Adjusted relativ risk (RR) for prescription of secundary medical prevention according to gender and age 6 months after primary vascular reconstruction according to hospitalisation periode: Early (1996-2007)

	Males 40-≤60years	Males 60-≤80 years	Males > 80years	females 40-≤60years	Females 60-≤80years
ACE/ATII					
1996-2000 %	51.7%	47.9%	21.1%	45.6%	48.6%
Adj. RR	1	1.04[0.98;1.10]	0.81[0.72;0.92]	0.89[0.80;0.98]	0.99[0.90;1.08]
2001-2007 %	45.4%	53.5%	39.2%	39.4%	51.7%
Adj. RR	1	1.06[0.98;1.14]	0.82[0.71;0.96]	0.85[0.77;0.93]	1.02[0.94;1.11]
Beta Blockers					
1996-2000 %	36.4%	33.1%	17.8%	35.5%	35.1%
Adj. RR	1	0.90[0.80;1.01]	0.58[0.42;0.79]	0.96[0.84;1.09]	0.99[0.87;1.12]
2001-2007 %	29.6%	35.7%	27.0%	30.9%	34.1%
Adj. RR	1	0.97[0.87;1.08]	0.72[0.59;0.88]	0.99[0.88;1.12]	0.92[0.82;1.12]
Calcium antagonists					
1996-2000 %	38.3%	36.6%	22.7%	39.8%	46.3%
Adj. RR	1	0.89[0.80;0.99]	0.61[0.47;0.80]	1.04[0.92;1.17]	1.15[1.03;1.29]
2001-2007 %	27.7%	33.2%	25.9%	29.5%	38.0%
Adj. RR	1	1.08[0.96;1.20]	0.85[0.69;1.04]	1.03[0.91;1.17]	1.20[1.07;1.35]
Diuretics					
1996-2000 %	50.0%	69.7%	79.8%	63.4%	79.2%
Adj. RR	1	1.20[1.12;1.30]	1..27[1.15;1.41]	1.23[1.13;1.33]	1.33[1.24;1.44]
2001-2007 %	34.7%	54.9%	72.1%	45.0%	63.5%
Adj. RR	1	1.26[1.15;1.37]	1.39[1.24;1.55]	1.21[1.10;1.33]	1.37[1.25;1.49]
Anti-platelet therapy					
1996-2000 %	75.1%	75.7%	66.8%	81.3%	79.6%
Adj. RR	1	1.00[0.95;1.05]	0.91[0.82;]1.02]	1.07[1.02;1.13]	1.06[1.01;1.12]
2001-2007 %	75.6%	78.6%	72.5%	80.0%	81.6%
Adj. RR	1	1.02[0.98;1.07]	0.97[0.90;1.05]	1.05[1.00;1.09]	1.05[1.01;1.09]
Lipid-lowering drugs					
1996-2000 %	58.7%	33.7%	3.6%	61.8%	38.0%
Adj. RR	1	0.68[0.62;0.75]	0.20[0.10;0.40]	1.07[0.99;1.16]	0.86[0.78;0.95]
2001-2007 %	72.3%	65.5%	35.4%	75.5%	69.7%
Adj. RR	1	0.93[0.89;0.98]	0.71[0.62;0.81]	1.06[1.01;1.12]	1.04[0.99;1.09]
Combination therapy**					
1996-2000 %	47.9%	30.5%	3.2%	52.3%	35.0%
Adj. RR	1	0.71[0.64;0.79]	0.19[0.09;0.38]	1.09[0.99;1.20]	0.90[0.80;1.00]
2001-2007 %	54.8	63.4%	38.0%	60.8%	66.9%
Adj. RR	1	1.09[1.02;1.15]	0.86[0.75;0.98]	1.11[1.04;1.19]	1.18[1.10;1.25]

**Combination therapy: Lipid-lowering, anti platelet, and at least one blood pressure lowering treament

4.2 Results study II

Patients characteristics at inclusion were compared between early (1996 to 2000, n=6,626) and late (2001 to 2006, n=9,866) time periods (Table of patients characteristics are displayed in the original manuscript included in the appendix). The proportions of central interventions were found to be higher in the late period, this was primarily explained by an increase in the access to percutaneous transluminal angioplasty in the iliac artery (early period vs. late period: 18.3% vs. 30.9%, respectively). No major differences in indication for primary vascular reconstruction were observed during the study period. The use of lipid-lowering drugs increased from 32.2% in 1996 to 76.1% in 2006 (adjusted RR 1.95, 95% CI 1.81-2.10). The

overall use of antihypertensive therapy was unchanged during the study period, but treatment shifted from diuretics/calcium antagonists towards ACE/ATIIs. The use of combination therapy increased from 29.1% in 1996 to 67.6% in 2006 (adjusted RR 1.95, 95% CI 1.80-2.12). This shift in the use of secondary medical prevention was independent of socio-demographic and clinical factors (minor changes were observed due to adjustment for expected confounding); see table 5. The pattern observed in the overall analyses remained when the analyses were stratified according to the county of residence. No major differences in the use of secondary medical prevention were observed between counties (data not shown).

Table 5 Adjusted relative risk (RR) for the prescription rate of secondary medical prevention six months after primary vascular reconstruction

	1996	2000	2006
ACE/ATII, % Crude RR Adj. RR	42.7 1 1	50.2 1.17 [1.08-1.27] 1.26 [1.17-1.37]	50.9 1.19 [1.11-1.28] 1.08 [1.01-1.17]
Beta-blockers, % Crude RR Adj. RR	31.2 1 1	36.1 1.16 [1.04-1.29] 1.22 [1.10-1.37]	32.2 1.03 [0.93-1.14] 0.95 [0.86-1.06]
Calcium antagonist, % Crude RR Adj. RR	39.6 1 1	38.7 0.98 [0.89-1.07] 1.01 [0.92-1.12]	31.2 0.79 [0.72-0.86] 0.73 [0.66-0.80]
Diuretics, % Crude RR Adj. RR	73.5 1 1	68.3 0.93 [0.89-0.98] 0.99 [0.94-1.04]	49.8 0.68 [0.64-0.72] 0.68 [0.64-0.71]
Anti platelet drugs, % Crude RR Adj. RR	74.5 1 1	80.3 1.08 [1.03-1.12] 1.08 [1.04-1.13]	81.8 1.10 [1.06-1.14] 1.07 [1.03-1.11]
Lipid lowering drugs, % Crude RR Adj. RR	32.6 1 1	48.4 1.48 [1.35-1.63] 1.39 [1.27-1.51]	76.1 2.33 [2.16-2.52] 1.95 [1.81-2.10]
Combination therapy, % Crude RR Adj. RR	29.1 1 1	42.7 1.46 [1.32-1.62] 1.43 [1.30-1.58]	67.6 2.32 [2.13-2.52] 1.95 [1.80-2.12]

Adjusted for age, sex, the Charlson comorbidity index, socioeconomic status (gross income, education level, marital status and employment), smoking, acute/elective surgery, discharge destination and patency at discharge.

4.3 Results of study III

We included 17495 matched patients (4912 ACE inhibitor users and 12583 non-users) with a median follow-up period of 582 days (range 30 to 4379 days). Table 6 displays the absolute risk of the competing outcomes and the corresponding adjusted HRs with 95% CIs, for which the non users serving as the reference group. The overall all cause mortality was 18.3%. ACE inhibitor use was associated with a significant lower mortality risk compared to non users (adj.HR 0.87, 95% CI 0.80-0.95). In contrast, no significant association were found concerning the risk of stroke or major amputation, whereas the risk of hospitalisation with MI and the risk of recurrent vascular surgery were increased (Adj.HR 1.22, 95% CI 1.05-1.42 and adj.HR 1.21, 95% CI 1.13-1.30).

All of the analyses were also preformed on the entire non matched population and the results were comparable to the results from the propensity score matched population (data not shown). Thus, the adj. HRs for all-cause mortality was less than 1.00 for all of the examined subgroups when comparing ACE/ATII users with non users. Similarly, the adj. HRs of MI and recurrent vascular surgery were

Table 6 Adjusted HR with 95% CIs for competing clinical outcomes according to ACE/ATII use among the entire study population (n=18,527) and the propensity score matched population (n=17,495)

	Entire study population		Propensity score matched population	
	% events	Adjusted HR a, b (95% CI)	% events	Adjusted HR a, b (95% CI)
All-cause mortality	18.2%	0.87 [0.78;0.95]	18.3%	0.87 [0.80;0.95]
MI	5.3%	1.17 [1.02;1.35]	5.1%	1.22 [1.05;1.42]
Stroke	6.5%	1.03 [0.89;1.20]	5.4%	1.01 [0.87;1.18]
Major amputation	9.1%	1.07 [0.95;1.20]	8.2%	1.06 [0.94;1.19]
Recurrent vascular surgery	23.3%	1.21 [1.13;1.30]	23.3%	1.21 [1.13;1.30]

a Adjusted for age, Charlson co-morbidity index, socioeconomic status (gross income, education level, marital status and employment), smoking status, acute/non-acute surgery, operation type, indication for operation discharge destination and patency at discharges and drug use during follow-up (angiotensin II receptor antagonists, beta-blockers, calcium antagonists, diuretics, anti platelet drugs and lipid-lowering drugs)

b Non users as the references

Table 7 Adjusted HR with 95% CIs for competing clinical outcomes according to ACE/ATII use among the entire study population (n=17,495), stratified according to prior MI or diabetes

	+ MI % n=1641	+MI adj. HR a, b (95% CI)	- MI n=15854	- MI adj. HR a, b (95% CI)
All-cause mortality	21.2%	0.96 [0.75;1.22]	18.0%	0.85 [0.78;0.94]
Myocardial infarct	11.3%	1.38 [1.01;1.89]	5.5%	1.17 [0.99;1.39]
Stroke	6.9%	1.14 [0.75;1.73]	5.3%	0.99 [0.85;1.17]
Major amputation	8.6%	1.22 [0.85;1.75]	8.9%	1.04 [0.91;1.18]
Recurrent vascular surgery	20.0%	1.17 [0.92;1.48]	23.7%	1.22 [1.13;1.32]
	+ DM % n=1664	**+DM adj. HR a,b (95% CI)**	**- DM N=15831**	**- DM adj. HR a, b (95% CI)**
All-cause mortality	18.6%	0.87 [0.68;1.12]	18.2%	0.86 [0.78;0.94]
Myocardial infarct	6.6%	1.27 [0.85;1.90]	5.0%	1.23 [1.05;1.44]
Stroke	5.8%	0.93 [0.66;1.45]	5.4%	1.01 [0.86;1.19]
Major amputation	20.1%	0.92 [0.73;1.17]	7.7%	1.09 [0.95;1.25]
Recurrent vascular surgery	23.4%	0.99 [0.80;1.23]	23.3%	1.25 [1.16;1.35]

a Adjusted as in table 6
b Non users as the references

greater than 1.00 in all of the examined subgroups, with the exception of recurrent vascular surgery in patients with diabetes.

4.4 Results of study IV

We included 16,945 matched patients (7,828 beta blocker users and 9,117 non-users) with a median follow-up period of 582 days (range 30 to 4,379 days).

Table 8 Crude and adj. HR with 95% CIs for competing adverse clinical outcomes according to of beta blocker in the entire population (n=18,527) and propensity score matched population (n=16,945**)**

	Entire study population		Propensity score matched population	
	% events	Adjusted HR a, b (95% CI)	% events	Adjusted HR a, b (95% CI)
All-cause mortality	18.2%	0.95 [0.86;1.05]	17.9%	0.92 [0.84;1.02]
MI	5.3%	1.38 [1.18;1.60]	5.3%	1.52 [1.31;1.78]
Stroke	5.5%	1.16 [0.98;1.37]	5.6%	1.21 [1.03;1.43]
Major amputation	9.1%	0.83 [0.72;0.95]	9.2%	0.80 [0.70;0.93]
Recurrent vascular surgery	23.3%	1.00 [0.86;1.05]	23.1%	0.99 [0.91;1.07]

a Adjusted for age, Charlson's co-morbidity index, socioeconomic status (gross income, education level, marital status and employment), smoking, acute/non-acute surgery, operation type, indication for operation discharge destination and patency at discharges as well as drug use during follow-up (ACE/ATII, calcium antagonists, diuretics, anti-platelet drugs and lipid-lowering drugs)
b Non users as the references

Table 8 displays the absolute risk of the competing outcomes and the corresponding adjusted HRs with 95% confidence intervals, for which the non users served as the reference group. The cumulative risk for major amputation was 23.1% (adj. HR 0.80; 95% CI 0.70 - 0.93), whereas the cumulative risk for MI and stroke were 5.3% and 5.6%, respectively (adj. HR for MI was 1.52, 95% CI 1.31-1.78 and adj. HR for stroke was 1.21, 95% CI 1.03-1.43). No differences related to all cause mortality or recurrent vascular surgery was observed between beta blocker users and non users.

Table 9 Crude and adjusted hazard ratios with 95% CIs for competing adverse clinical outcomes according to use of beta blockers the propensity core matched population (n=16945), stratified to prior MI or stroke

	All-cause mortality	MI	Stroke	Major amputation	Recurrent vascular surgery
- MI a, b n=15218 Adj. HR (95%CI)	17.5% 0.92 [0.82;1.02]	4.6% 1.58 [1.32;1.89]	5.3% 1.15 [0.95;1.38]	9.3% 0.77 [0.66;0.90]	23.5% 1.00 [0.91;1.10]
+ MI a, b n=1727 Adj. HR(95% CI)	21.1% 0.79 [0.75;1.24]	11.3% 1.10 [0.80;1.52]	7.1% 1.63 [1.09;2.44]	8.9% 1.05 [0.72;1.53]	20.2% 1.02 [0.80;1.29]
- Stroke a, b n=15087 Adj. HR(95% CI)	17.6% 0.93 [0.84;1.04]	5.1% 1.59 [1.35;1.89]	5.1% 1.25 [1.04;1.50]	8.8% 0.80 [0.68;0.93]	26.2% 1.02 [0.94;1.12]
+ Stroke a, b n=1858 Adj. HR(95% CI)	19.9% 0.89 [0.67;1.18]	6.5% 1.13 [0.74;1.73]	8.6% 1.00 [0.68;1.49]	12.3% 0.90 [0.63;1.28]	22.8% 0.77 [0.60;0.99]

a Adjusted as in table 8

b Non users as the references

stratifying the population according to prior MI, we found that beta blocker users without prior MI had an increased risk of recurrent MI (adj. HR 1.58; 95% CI 1.32-1.89), whereas no differences were observed among beta blocker users with prior MI (adj. HR 1.10; 95% CI 0.80-1.52). We also found that beta blocker users with prior MI had an increased risk of recurrent stroke (adj. HR 1.63; 95% CI 1.09-2.44), whereas the risk for beta blocker users without prior MI remained unchanged (see table 9).

5. DISCUSSION

5.1 Strengths and limitations of the methodology

To review the validity of our estimates, it was necessary to consider whether the association between the expected cause and effect was real or artificially. Factors that can influence this interpretation include the selection of the study population, the collection of data related to exposures, the outcomes, potential confounding factors and statistical precision. Figure 8 outlines these alternative explanations. It is therefore necessary to evaluate alternatives to causal relation before interpreting the study findings as evidence of causality.

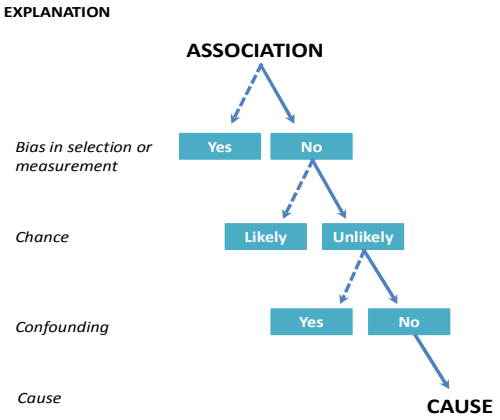
Selection biases are distortions of the results, which may develop from the selection of study participants and from the factors that influence on the study participation. In case of selection bias, the relation between exposure and outcome differs between those who participated and all those who in theory were eligible for the study. The loss of follow-up is also a potentially source of selection bias91. All studies in this thesis were based on nationwide population-based registers with high validity of data and almost 100% follow-up.

5.1.1 Selection problems

Vascular surgical activity in Denmark appears to be comparable to other Western Countries (14.4/100,000 inhabitants per year submitted to surgery), as well as other Western countries with vascular registries (according the Vascunet committee under ESVS, numbers provided by Dr. Leif Panduro Jensen). The similarity secures the external validity of our study, at least for vascular surgery populations that mimic the demographic and socio-economic factors of Scandinavian populations. 5.1.2 Misclassification problems (measurement bias).

It is well known that misclassification can occur during data collection in routine clinical settings; regarding both exposures and out

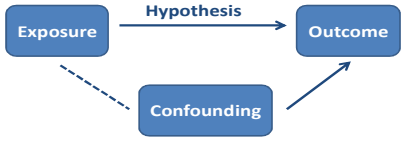
Figure 8 Associations and cause from Fletcher `Clinical Epidemiology The essentials´91



comes. Non-differential misclassification (error evenly distributed between comparison groups) will mostly produce a bias towards the null hypothesis; in contrast a differential misclassification (error unevenly distributed between comparison groups) can lead to either an over- or under estimation of the true association109.
The data from the Danish Vascular Registry were collected prospectively and independent of our studies, in preparation for surveillance, quality control and administration in a non-standardised setting during daily clinical work. Any misclassification that occurred would therefore most likely be non-differential. Furthermore, the accuracy of the Danish Vascular Registry was previously described as good93, and our validation confirmed this assessment. To assess the data validity of the Danish Vascular Registry, we compared information recorded in the registry to information recorded in the medical records of 200 randomly selected patients. We found discrepancies in less than 1% of cases for most variables, including patency at discharge, and in less than 3% of cases regarding the type of vascular reconstruction. We also compared The Danish Vascular Registry with the Danish Patient Registry, and good concordance was found (no mismatch concerning operations-date and -code, information on former vascular surgery, or patency at discharge).
Data regarding the use of secondary medical prevention (exposures) were collected independently of the outcomes from several different registries; thus, any misclassification would most likely be non-differential. The fact that low-dose aspirin does not require a prescription may have caused a differential misclassification, and this misclassification may have occurred because patients with low comorbidity score likely receive aspirin without a prescription (which implies that their expenses are not reimbursed and that aspirin use is remains unrecorded) when compared with patients with high comorbidity scores. From the available data, it was not possible to determine whether a lack of drug use indicated that a drug had not been prescribed by a physician or that the patient did not fill the prescription at the pharmacy.
Data regarding the outcomes in studies III and IV were obtained from the Danish Civil Registration System (all cause mortality) and the Danish Patient Registry and the validity is considered to be high (see 3.1 data sources).

5.1.3 Confounding
Confounding may be considered as confusion of effects. To be a confounder, a variable must be associated with the exposure, be an extraneous risk factor for the outcome and it cannot be an intermediate step in the causal path between the exposure and the outcome. In figure 9 the arrows illustrates a hypothesised association, whereas the dotted line illustrates a causal or non-causal relationship.
Our study population consisted of patients with a universal cardiovascular disease and numerous social as well as economic factors that could have influenced their use of secondary medical prevention and thereby interfered with the clinical outcomes expected. Detailed information concerning a range of potential confounding factors was available for our study population, and there were several methods that could be used to account for confounding factors in observational studies. We used the methods of restriction, matching, stratification and adjustment in multivariable regression analyses91;109.

Figure9 Model of interaction between confounding factores109



In all four studies we restricted the study population by excluding patients younger than 40 years of age and patients who died within 30 days of discharges after primary vascular reconstruction. We also excluded patients undergoing primary vascular reconstruction or major amputation due to infection, cancer or trauma. We used the Charlson comorbidity index because it totals the burden of comorbidity, although the index does not reflect the severity of individual co-morbidities. Thus, even if a patient has several wrong or missing diagnoses, the classification according to the Carlson's comorbidity index can still be correct98.
In studies 3 and 4, the use of ACE/ATII and beta blockers was not randomly assigned in the study population leading us to use propensity score matching (see the statistical methods section)102;107. Stratification was used in study 3 and 4 to outline the remaining distribution difference for MI and stroke prior to primary vascular reconstruction.
We present both the crude and the adjusted estimates to show the magnitude of the confounding by the included covariates. In study 3 and 4 the propensity score matching was followed by Cox-regression analysis which enables us to adjust for potential residual confounding, using non users as the reference point.

5.1.4 Precision
In all our main analyses, the large size of the study population resulted in high statistical precision, as a narrow 95 % confidence interval was generally detected. However, some caution could be taken when interpreting the findings of the sub-analyses due to the use of extended stratification and consequently fewer included observations (e.g., in study 1, we excluded patients who were > 80 years of age from the multivariable analysis concerning 10 years study period, as the numbers were too small to for a meaningful comparison). It is not possible to eliminate random error completely

in studies based on clinical observations. Therefore, residual or unaccounted for confounding may have influenced our findings, despite our attempts to minimize the likely-hood of such occurrence.
The major strengths of our studies include the population-based design, the availability of detailed prospectively collected individual-level data and complete follow-up. We used restriction, matching, stratification and adjustment in multi-variable regression analyses to minimize the risk of bias and/or confounding. In studies III and IV, the two-step statistical procedure makes the model-based inferences considerably less model dependent and generally more accurate. However, despite our attempt to minimize bias and confounding some residual confounding still may occur.

5.2 Major findings and comparison with existing literature

5.2.1 Study I
Our findings of moderate to low use of secondary medical prevention among symptomatic PAD patients in Denmark between 1996 and 2006 was consistent with previous smaller Danish studies82;110;111 as well as international studies1;76.
To our knowledge, no previous studies have explored the potential existence and magnitude of age-related differences related to the use of secondary medical prevention among PAD patients. However, age-related differences have previously been observed among patients with ischaemic stroke86;112;113 and MI87, which indicates that age-related differences are frequent among patients with cardiovascular disease. Gender-related differences related to the use of secondary medical prevention have previously been reported among PAD patients, as men have been showing to have a greater likelihood of receiving lipid-lowering therapy, anti platelet therapy, ACE/ATII and beta blockers, in comparison with women25;80. However, in contrast to these findings, women generally demonstrated greater likelihood of receiving secondary medical prevention in our study, although these differences were modest and did not reach statistical significance. This inconsistency between studies may reflect differences in the median age and the stage of PAD in the studied populations.
We found that the age- and gender-related differences in the use of secondary medical prevention have disappeared or at least substantially decreased, in recent years. This positive development parallels the publication of clinical guidelines recommending the routine use of secondary medical prevention to all the PAD patients regardless of age and gender12;17-19.

5.2.2 Study II
Our study spanned a decade during which the evidence for and attitudes towards the use of secondary medical prevention in PAD patients changed markedly. The first Trans-Atlantic Inter-Society Consensus (TASC I)100 recommended the use of aspirin and statins for all PAD patients in 2000, and recommendations for the use of heart rate- and blood pressure-lowering agents were added in 2007 (TASC II)12. Specific Danish guidelines were first published in 200519. We found a substantial increase in the use of lipid-lowering drugs and combination therapy (concomitant filling of prescriptions for lipid-lowering, antiplatelets, and at least one blood pressure lowering treatment) among Danish PAD patients who underwent primary vascular reconstruction between 1996 and 2006. However, the publication of clinical guidelines does not necessarily lead to improvements in medical care, although improvements can be achieved when guidelines are introduced in the context of rigorous evaluations114.
Previously, substantial geographic international and national variations in the use of secondary medical prevention have been reported25;88. Our study we did not identify substantial differences in pharmacological according to location of residence, although this lack of any major variation across Danish counties may not reflect an absence of geographic variation at a more local level. Nevertheless, our findings indicate that the overall population was offered similar healthcare services regardless of the administrative area of residence.

5.2.3 Study III
In this nationwide follow-up study that evaluated all patients undergoing primary vascular reconstruction in Denmark over a 10 years period, we found that the use of ACE/ATII was associated with a lower all cause mortality risk. These findings are in accordance with previous studies based on selected patient populations38;92.
In contrast to earlier reports38;40, we also found ACE/ATII use to be associated with an increased risk of MI and the need for recurrent vascular surgery. When interpreting these somewhat surprising findings, it should be noted that MI in this context was defined as hospitalization due to MI: Patients dying from MI before reaching a hospital were therefore not classified as MI. The increased risk of MI in our study may therefore reflect the fact that ACE/ATII users have a lower risk of dying from MI prior to hospitalisation and therefore have a corresponding higher risk of hospitalisation due to MI or other competing outcomes. This hypothesis is supported by the findings of two cross-sectional studies concluding that prior ACE/ATII use is associated with lower troponin release and lower infarct volume in patients with acute coronary syndrome 48;49.
In addition, we found an increased risk of recurrent vascular surgery for ACE/ATII users. To our knowledge, no previous studies have examined the association between the use of ACE/ATII and the risk of recurrent vascular surgery in patients with PAD. Because our study was of an observational nature, we cannot exclude the possibility that this association may reflect unaccounted or residual confounding. Recurrent vascular surgery is not a direct measurement of the severity of PAD but is rather due to the combination of patient´s requirements and the willingness of the vascular surgeon to perform a new procedure.
ACE inhibitors can improve peripheral blood pressure in PAD patients47;115 and ramipril was shown to prevent major cardiovascular events in patients with clinical, as well as subclinical, PAD in the Heart Outcomes Prevention Evaluation (HOPE) study38;40. Additionally, Sigvant et al. found ACE inhibitors to be cost-effective in asymptomatic PAD patients because they resulted in decreased cardiovascular events39. The reduced all cause mortality found in our study supports the hypothesis that these experimental findings can also translate into important clinical benefits in real life clinical settings among unselected patients (for more information, see further discussion of ACE/ATII use in PAD patients in section 1.4.2.).

5.2.4 Study IV
In this nationwide follow-up study over a 10 years period, based on all patients undergoing primary vascular reconstruction in Denmark, we found beta blocker use to be associated with a 20% significant lower risk of major amputation compared to non users. Previous reports concludes, that beta blocker use are safe for PAD patients concerning beta blockers suspected negative effects on walking capacity and impairment of intermittent claudication 33;52;53. Our findings of the reduced risk of future major amputation are indirectly accordance with these rapports, though the influences of beta

blocker use on amputation rate have, to our knowledge, not been described previously.
Our finding of beta blockers overall being associated with an increased risk of MI and/or stroke, during the follow-up period, was not in line with previous studies including studies on symptomatic PAD patients with prior MI54;116. These conflicting findings may possibly reflect residual confounding, despite our attempt to minimize bias and /or confounding factors by statistical adjustment and study design. However, it should be noted that a recent systematic review showed that high dose beta blockers increased the systolic blood pressure variability, which is a powerful risk factor for stroke117.
Randomized clinical trials have previously found that beta blocker use following MI in symptomatic PAD patients is associated with a significant reduction in early and late mortality118;119. We could not confirm this finding in our study, which is most likely an indicator of residual or unaccounted confounding. (for more information, see further discussion of beta blocker use in PAD patients in section 1.4.3.).

6. CONCLUSIONS

6.1 Study I

We found evidence for moderate to low use of secondary medical prevention in Denmark which is in contrast to the recommendations off clinical guide-lines. However, we found that the use of secondary medical prevention increased during the study period. Moreover, substantial age- related, and to some extent, also gender-related, differences in the use of secondary medical prevention, were observed in the late 1990s, although these differences appeared to decrease during the study period. Continuous efforts are warranted to ensure optimal secondary medical prevention among PAD patients who undergo primary vascular reconstruction, regardless of age and gender.

6.2 Study II

The use of evidence-based secondary medical prevention, especially lipid-lowering drugs, increased substantially among symptomatic PAD patients in Denmark from 1996 to 2006. This shift in the use of secondary medical prevention was independent of socio-demographic and clinical factors. Moreover, no substantial differences in pharmacological use related to the location of residence, were observed. However, recommendations in current clinical guidelines suggest that room for improvement remains.

6.3 Study III

In the study population of patients undergoing primary vascular reconstruction between 1996 and2007, we found the use of ACE inhibitors to be associated with lower all cause mortality but also increased long-term risk of MI and recurrent vascular surgery.

6.4 Study IV

Beta blocker use after primary vascular surgery was associated with a lower risk of major amputation, but also an increased risk of hospitalization with MI and stroke. No associations between beta blocker use and all cause mortality or the risk of recurrent vascular surgery was found.

7. PERSPECTIVES

PAD is a common manifestation of systematic atherosclerosis and the prevalence of PAD is expected to increase substantially, due to ongoing ageing of the population across most of the world20-22. Previously, several studies have indicated that the use of secondary medical prevention generally is insufficient among PAD patients25;35;73-78. Additionally, it is well documented that the presence of PAD increases the risk of cardiovascular events including major limb loss, MI, stroke and death1;2;4;16. This thesis confirms these findings, though we also showed an increase of the usage of secondary medical prevention during the study period, independently of socio-demographic and clinical factors. Our results underline an important need to ensure an adequate implementation of evidence-based recommendations for the use of secondary medical prevention, independently of age and gender.
In the light of this findings, follow-up on the usages of secondary medical prevention among symptomatic PAD patients are essential to ensure persistent focus on the subject. However, if adequate implementation, of long-term secondary medical prevention, is achieved in the future, it could represent a major economic burden to the health care system. Therefore, studies are needed to evaluate the cost-effectiveness of the use of secondary medical prevention, among patients after primary vascular reconstruction, as previously done for asymptomatic PAD patients39.
This thesis documents effectiveness of ACE/ATII and beta blocker use, among patients who underwent primary vascular reconstruction. We found ACE/ATII use to be associated with lower all cause mortality, while no association between beta blocker use and all cause mortality was found. However, both ACE/ATII and beta blocker use were associated with increased long-term risk of cardiovascular events. Our results are complex, but important because blood pressure lowering treatment is a key component in the secondary medical prevention, also regarding symptomatic PAD patients. Traditionally, the medical treatment of PAD patients has in most health care systems no affiliation to a well-defined dedicated speciality, as patients with ischaemic stroke and acute coronary syndrome. The vascular surgeon takes care of the peri-operative pharmacologic treatment, whereas the general practitioner undertakes the recurrent secondary medical prevention after discharge. A multidisciplinary approach concerning blood pressure treatment among symptomatic PAD patients are desirable, in the future.
Future evaluation of other blood pressure lowering treatments as well as combination therapies (lipid lowering drugs, anti-platelets therapy and any blood pressure lowering treatment) are required, whit the goal of decreasing the burden of clinical outcomes in symptomatic PAD patients. Furthermore, it would be of great clinical relevance to identify patients experiencing the impact of optimal secondary medical prevention, by a nested set of variables (concerning socio-economic factors, operation type and comorbidity).
The hope is that the findings in this thesis will contribute to continuous improvement in the usage of secondary medical prevention, among patients who underwent primary vascular reconstruction, and thereby causing a reduction in the burden of cardiovascular events for this high-risk population.

8. SUMMARY

Peripheral arterial disease (PAD) is a common manifestation of symptomatic atherosclerosis that leads to a significantly elevated risk of cardiovascular events, including major limb loss, myocardial infarction, stroke and death. The prevalence proportions of PAD increase dramatically with age and appear to progress more aggressively in women than in men. Several studies have indicated that the use of secondary medical prevention is generally insufficient among PAD patients. However, current national and international guide-

lines recommend lipid-lowering and anti-platelet therapy, supplemented with aggressive blood pressure lowering treatment.
We aimed to determine whether there were age-, gender-, geography or time related differences in the use of secondary medical prevention, following primary vascular reconstruction. We also sought to describe the prognoses for the same population, according to the association between the use of ACE/ATII inhibitors (angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists) or beta blockers and clinical outcomes (all cause mortality, myocardial infarction, stroke, major amputation and/or recurrent vascular surgery) in a population-based, long-term follow-up study.
We established a data base by linking four population based administrative and health-care registries. All Danish patients undergoing primary vascular surgical reconstruction due to atherosclerotic disease between 1997 and 2007 were included and identified in the Danish Vascular Registry; a total of 20,761 patients were followed during a median of 582 days (range of 30 to 4,379 days). Data regarding all prescriptions filled by the study population were obtained from the Medical Registry of the Danish Medicines Agency.
Study I: Age- and gender-related differences. We found moderate to low use of secondary medical prevention. However, this use has increased in recent years and the age- and gender-related differences in use have been reduced or eliminated.
k geographic or time related differences. The use of evidence-based secondary medical prevention, especially lipid-lowering drugs, increased substantially over time, regardless of socio-demographic and clinical factors. No substantial differences in pharmacological use according to location of residence were observed.
Study III: Use of ACE/ATII and prognosis. We found the use of ACE inhibitors to be associated with lower all cause mortality but also an increased long-term risk of recurrent vascular reconstruction and myocardial infarction.
Study IV: Use of beta blockers and prognosis. We found beta blocker use to be associated with a lower risk of major amputation, but also an increased risk of new myocardial infarction and stroke. No association were found regarding all cause mortality or the risk of recurrent vascular surgery.
In conclusion, the use of secondary medical prevention following primary vascular surgery (between 1996 and 2006 in Denmark) shifted towards a more evidence-based treatment, as reduction in age-, gender- and geography related differences were observed early in the study period. However, recommendations for the current clinical guidelines suggest that additional improvement can be made.
The treatment of hypertension in PAD patients is complex, and our results are also complex but indicate that ACE/ATII and beta blockers are safe for use in symptomatic PAD patients.

10. REFERENCES

(1) Aronow WS, Ahmed MI, Ekundayo OJ, Allman RM, Ahmed A. A propensity-matched study of the association of peripheral arterial disease with cardiovascular outcomes in community-dwelling older adults. *Am J Cardiol* 2009; 103(1):130-135.

(2) Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* 1992; 326(6):381-386.

(3) Criqui MH, Denenberg JO. The generalized nature of atherosclerosis: how peripheral arterial disease may predict adverse events from coronary artery disease. *Vasc Med* 1998; 3(3):241-245.

(4) Diehm C, Schuster A, Allenberg JR, Darius H, Haberl R, Lange S et al. High prevalence of peripheral arterial disease and co-morbidity in 6880 primary care patients: cross-sectional study. *Atherosclerosis* 2004; 172(1):95-105.

(5) Murabito JM, Evans JC, Nieto K, Larson MG, Levy D, Wilson PW. Prevalence and clinical correlates of peripheral arterial disease in the Framingham Offspring Study. *Am Heart J* 2002; 143(6):961-965.

(6) Weitz JI, Byrne J, Clagett GP, Farkouh ME, Porter JM, Sackett DL et al. Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. *Circulation* 1996; 94(11):3026-3049.

(7) Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA* 2008; 300(2):197-208.

(8) Stansby G, Mister R, Fowkes G, Roughton M, Nugara F, Brittenden J et al. High risk of peripheral arterial disease in the United kingdom: 2-year results of a prospective registry. *Angiology* 2011; 62(2):111-118.

(9) Lee AJ, Price JF, Russell MJ, Smith FB, van Wijk MC, Fowkes FG. Improved prediction of fatal myocardial infarction using the ankle brachial index in addition to conventional risk factors: the Edinburgh Artery Study. *Circulation* 2004; 110(19):3075-3080.

(10) Resnick HE, Lindsay RS, McDermott MM, Devereux RB, Jones KL, Fabsitz RR et al. Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality: the Strong Heart Study. *Circulation* 2004; 109(6):733-739.

(11) Doobay AV, Anand SS. Sensitivity and specificity of the ankle-brachial index to predict future cardiovascular outcomes: a systematic review. *Arterioscler Thromb Vasc Biol* 2005; 25(7):1463-1469.

(12) Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg* 2007; 45 Suppl S:S5-67.

(13) Criqui MH, Fronek A, Barrett-Connor E, Klauber MR, Gabriel S, Goodman D. The prevalence of peripheral arterial disease in a defined population. *Circulation* 1985; 71(3):510-515.

(14) Fowkes FG, Housley E, Cawood EH, Macintyre CC, Ruckley CV, Prescott RJ. Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease

in the general population. *Int J Epidemiol* 1991; 20(2):384-392.

(15) FONTAINE R, KIM M, KIENY R. [Surgical treatment of peripheral circulation disorders]. *Helv Chir Acta* 1954; 21(5-6):499-533.

(16) Welten GM, Schouten O, Hoeks SE, Chonchol M, Vidakovic R, van Domburg RT et al. Long-term prognosis of patients with peripheral arterial disease: a comparison in patients with coronary artery disease. *J Am Coll Cardiol* 2008; 51(16):1588-1596.

(17) Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation* 2006; 113(11):e463-e654.

(18) De BG, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J et al. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force Of European and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of eight societies and by invited experts). *Arch Mal Coeur Vaiss* 2004; 97(10):1019-1030.

(19) Schroder TV, Ebskov LB, Egeblad M, Husted S, Jelnes R, Jensen T et al. Underekstremitetsiskæmi, forebyggelse og behandling. 2. 2005. Den almindelige Danske Lægeforening.
Ref Type: Report

(20) Alzamora MT, Baena-Diez JM, Sorribes M, Fores R, Toran P, Vicheto M et al. Peripheral Arterial Disease study (PERART): prevalence and predictive values of asymptomatic peripheral arterial occlusive disease related to cardiovascular morbidity and mortality. *BMC Public Health* 2007; 7:348.

(21) Hiatt WR, Hoag S, Hamman RF. Effect of diagnostic criteria on the prevalence of peripheral arterial disease. The San Luis Valley Diabetes Study. *Circulation* 1995; 91(5):1472-1479.

(22) Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. *Circulation* 2004; 110(6):738-743.

(23) Statistics Denmark. Danmark i tal 2010. 2012.

(24) Murabito JM, d'Agostino RB, Silbershatz H, Wilson WF. Intermittent claudication. A risk profile from The Framingham Heart Study. *Circulation* 1997; 96(1):44-49.

(25) Sigvant B, Wiberg-Hedman K, Bergqvist D, Rolandsson O, Wahlberg E. Risk factor profiles and use of cardiovascular drug prevention in women and men with peripheral arterial disease. *Eur J Cardiovasc Prev Rehabil* 2009; 16(1):39-46.

(26) Sigvant B, Lundin F, Nilsson B, Bergqvist D, Wahlberg E. Differences in presentation of symptoms between women and men with intermittent claudication. *BMC Cardiovasc Disord* 2011; 11:39.

(27) McDermott MM, Greenland P, Liu K, Criqui MH, Guralnik JM, Celic L et al. Sex differences in peripheral arterial disease: leg symptoms and physical functioning. *J Am Geriatr Soc* 2003; 51(2):222-228.

(28) Vouyouka AG, Kent KC. Arterial vascular disease in women. *J Vasc Surg* 2007; 46(6):1295-1302.

(29) Beard J.D., Gaines P.A. Vascular and endovascular surgey. fourth ed. 2009.

(30) Feringa HH, van Waning VH, Bax JJ, Elhendy A, Boersma E, Schouten O et al. Cardioprotective medication is associated with improved survival in patients with peripheral arterial disease. *J Am Coll Cardiol* 2006; 47(6):1182-1187.

(31) De Buyzere ML, Clement DL. Management of hypertension in peripheral arterial disease. *Prog Cardiovasc Dis* 2008; 50(4):238-263.

(32) Mehler PS, Coll JR, Estacio R, Esler A, Schrier RW, Hiatt WR. Intensive blood pressure control reduces the risk of cardiovascular events in patients with peripheral arterial disease and type 2 diabetes. *Circulation* 2003; 107(5):753-756.

(33) Lane DA, Lip GY. Treatment of hypertension in peripheral arterial disease. *Cochrane Database Syst Rev* 2009;(4):CD003075.

(34) Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009; 338:b1665.

(35) Mukherjee D, Lingam P, Chetcuti S, Grossman PM, Moscucci M, Luciano AE et al. Missed opportunities to treat atherosclerosis in patients undergoing peripheral vascular interventions: insights from the University of Michigan Peripheral Vascular Disease Quality Improvement Initiative (PVD-QI2). *Circulation* 2002; 106(15):1909-1912.

(36) Radack K, Deck C. Beta-adrenergic blocker therapy does not worsen intermittent claudication in subjects with peripheral arterial disease. A meta-analysis of randomized controlled trials. *Arch Intern Med* 1991; 151(9):1769-1776.

(37) Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000; 342(3):145-153.

(38) Ostergren J, Sleight P, Dagenais G, Danisa K, Bosch J, Qilong Y et al. Impact of ramipril in patients with evidence of clinical or subclinical peripheral arterial disease. *Eur Heart J* 2004; 25(1):17-24.

(39) Sigvant B, Henriksson M, Lundin F, Wahlberg E. Asymptomatic peripheral arterial disease: is pharmacological prevention of cardiovascular risk cost-effective? *Eur J Cardiovasc Prev Rehabil* 2011; 18(2):254-261.

(40) Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000; 342(3):145-153.

(41) Ahimastos AA, Lawler A, Reid CM, Blombery PA, Kingwell BA. Brief communication: ramipril markedly improves walking ability in patients with peripheral arterial disease: a randomized trial. *Ann Intern Med* 2006; 144(9):660-664.

(42) Roberts DH, Tsao Y, Linge K, McLoughlin GA, Breckenridge A. Double-blind comparison of captopril with nifedipine in hypertension complicated by intermittent claudication. *Angiology* 1992; 43(9):748-756.

(43) Sonecha TN, Nicolaides AN, Kyprianou P, Zukowski A, Papadakis K, Vasdekis S et al. The effect of enalapril on leg muscle blood flow in patients with claudication. *Int Angiol* 1990; 9(1):22-24.

(44) Lonn EM, Yusuf S, Jha P, Montague TJ, Teo KK, Benedict CR et al. Emerging role of angiotensin-converting enzyme inhibitors in cardiac and vascular protection. *Circulation* 1994; 90(4):2056-2069.

(45) Mancini GB, Henry GC, Macaya C, O'Neill BJ, Pucillo AL, Carere RG et al. Angiotensin-converting enzyme inhibition with quinapril improves endothelial vasomotor dysfunction in patients with coronary artery disease. The TREND (Trial on Reversing ENdothelial Dysfunction) Study. *Circulation* 1996; 94(3):258-265.

(46) Ahimastos AA, Dart AM, Lawler A, Blombery PA, Kingwell BA. Reduced arterial stiffness may contribute to angiotensin-converting enzyme inhibitor induced improvements in walking time in peripheral arterial disease patients. *J Hypertens* 2008; 26(5):1037-1042.

(47) Hirsch AT, Duprez D. The potential role of angiotensin-converting enzyme inhibition in peripheral arterial disease. *Vasc Med* 2003; 8(4):273-278.

(48) Kennon S, Barakat K, Hitman GA, Price CP, Mills PG, Ranjadayalan K et al. Angiotensin-converting enzyme inhibition is associated with reduced troponin release in non-ST-elevation acute coronary syndromes. *J Am Coll Cardiol* 2001; 38(3):724-728.

(49) Shariff N, Dunbar C, Matsumura ME. Relation of pre-event use of inhibitors of the renin-angiotensin system with myocardial infarct size in patients presenting with a first ST-segment elevation myocardial infarction. *Am J Cardiol* 2010; 106(5):646-649.

(50) Staessen JA, Wang JG, Thijs L. Cardiovascular protection and blood pressure reduction: a meta-analysis. *Lancet* 2001; 358(9290):1305-1315.

(51) Abrams J. Clinical practice. Chronic stable angina. *N Engl J Med* 2005; 352(24):2524-2533.

(52) Radack K, Deck C. Beta-adrenergic blocker therapy does not worsen intermittent claudication in subjects with peripheral arterial disease. A meta-analysis of randomized controlled trials. *Arch Intern Med* 1991; 151(9):1769-1776.

(53) Paravastu SC, Mendonca DA, da SA. Beta blockers for peripheral arterial disease. *Eur J Vasc Endovasc Surg* 2009; 38(1):66-70.

(54) Aronow WS, Ahn C. Effect of beta blockers on incidence of new coronary events in older persons with prior myocardial infarction and symptomatic peripheral arterial disease. *Am J Cardiol* 2001; 87(11):1284-1286.

(55) Ostlund-Lindqvist AM, Lindqvist P, Brautigam J, Olsson G, Bondjers G, Nordborg C. Effect of metoprolol on diet-induced atherosclerosis in rabbits. *Arteriosclerosis* 1988; 8(1):40-45.

(56) Kaplan JR, Manuck SB, Adams MR, Clarkson TB. The effects of beta-adrenergic blocking agents on atherosclerosis and its complications. *Eur Heart J* 1987; 8(9):928-944.

(57) Dimmitt SB, Williams PD, Croft KD, Beilin LJ. Effects of beta-blockers on the concentration and oxidizability of plasma lipids. *Clin Sci (Lond)* 1998; 94(6):573-578.

(58) Boquist S, Ruotolo G, Hellenius ML, nell-Toverud K, Karpe F, Hamsten A. Effects of a cardioselective beta-blocker on postprandial triglyceride-rich lipoproteins, low density lipoprotein particle size and glucose-insulin homeostasis in middle-aged men with modestly increased cardiovascular risk. *Atherosclerosis* 1998; 137(2):391-400.

(59) Cruickshank JM. Beta-blockers, plasma lipids, and coronary heart disease. *Circulation* 1990; 82(3 Suppl):II60-II65.

(60) Webb AJ, Rothwell PM. Effect of dose and combination of antihypertensives on interindividual blood pressure variability: a systematic review. *Stroke* 2011; 42(10):2860-2865.

(61) LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005; 352(14):1425-1435.

(62) MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; 360(9326):7-22.

(63) Leng GC, Price JF, Jepson RG. Lipid-lowering for lower limb atherosclerosis. *Cochrane Database Syst Rev* 2000;(2):CD000123.

(64) Buchwald H, Bourdages HR, Campos CT, Nguyen P, Williams SE, Boen JR. Impact of cholesterol reduction on peripheral arterial disease in the Program on the Surgical Control of the Hyperlipidemias (POSCH). *Surgery* 1996; 120(4):672-679.

(65) Mohler ER, III, Hiatt WR, Creager MA. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. *Circulation* 2003; 108(12):1481-1486.

(66) Pedersen TR, Kjekshus J, Pyorala K, Olsson AG, Cook TJ, Musliner TA et al. Effect of simvastatin on ischemic signs and symptoms in the Scandinavian simvastatin survival study (4S). *Am J Cardiol* 1998; 81(3):333-335.

(67) Schillinger M, Exner M, Mlekusch W, Amighi J, Sabeti S, Muellner M et al. Statin therapy improves cardiovascular outcome of patients with peripheral artery disease. *Eur Heart J* 2004; 25(9):742-748.

(68) Antiplatelet therapy in peripheral arterial disease. Consensus statement. *Eur J Vasc Endovasc Surg* 2003; 26(1):1-16.

(69) Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; 324(7329):71-86.

(70) Cassar K, Bachoo P, Ford I, Greaves M, Brittenden J. Platelet activation is increased in peripheral arterial disease. *J Vasc Surg* 2003; 38(1):99-103.

(71) Goldhaber SZ, Manson JE, Stampfer MJ, LaMotte F, Rosner B, Buring JE et al. Low-dose aspirin and subsequent peripheral arterial surgery in the Physicians' Health Study. *Lancet* 1992; 340(8812):143-145.

(72) Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006; 354(16):1706-1717.

(73) Cacoub PP, Abola MT, Baumgartner I, Bhatt DL, Creager MA, Liau CS et al. Cardiovascular risk factor control and outcomes in peripheral artery disease patients in the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *Atherosclerosis* 2009; 204(2):e86-e92.

(74) Coveney AP, O'Brien GC, Fulton GJ. ACE up the sleeve - are vascular patients medically optimized? *Vasc Health Risk Manag* 2011; 7:15-21.

(75) Feringa HH, Bax JJ, Hoeks S, van Waning VH, Elhendy A, Karagiannis S et al. A prognostic risk index for long-term mortality in patients with peripheral arterial disease. *Arch Intern Med* 2007; 167(22):2482-2489.

(76) Flu HC, Tamsma JT, Lindeman JH, Hamming JF, Lardenoye JH. A systematic review of implementation of established recommended secondary prevention measures in patients with PAOD. *Eur J Vasc Endovasc Surg* 2010; 39(1):70-86.

(77) Monreal M, Alvarez L, Vilaseca B, Coll R, Suarez C, Toril J et al. Clinical outcome in patients with peripheral artery disease. Results from a prospective registry (FRENA). *Eur J Intern Med* 2008; 19(3):192-197.

(78) Muller-Buhl U, Laux G, Szecsenyi J. Secondary Pharmacotherapeutic Prevention among German Primary Care Patients with Peripheral Arterial Disease. *Int J Vasc Med* 2011; 2011:316496.

(79) Khan S, Flather M, Mister R, Delahunty N, Fowkes G, Bradbury A et al. Characteristics and treatments of patients with peripheral arterial disease referred to UK vascular clinics: results of a prospective registry. *Eur J Vasc Endovasc Surg* 2007; 33(4):442-450.

(80) Rice TW, Lumsden AB. Optimal medical management of peripheral arterial disease. *Vasc Endovascular Surg* 2006; 40(4):312-327.

(81) McDermott MM, Mehta S, Ahn H, Greenland P. Atherosclerotic risk factors are less intensively treated in patients with peripheral arterial disease than in patients with coronary artery disease. *J Gen Intern Med* 1997; 12(4):209-215.

(82) Gasse C, Jacobsen J, Larsen AC, Schmidt EB, Johannesen NL, Videbaek J et al. Secondary medical prevention among Danish patients hospitalised with either peripheral arterial disease or myocardial infarction. *Eur J Vasc Endovasc Surg* 2008; 35(1):51-58.

(83) Aronow WS, Ahmed MI, Ekundayo OJ, Allman RM, Ahmed A. A propensity-matched study of the association of peripheral arterial disease with cardiovascular outcomes in community-dwelling older adults. *Am J Cardiol* 2009; 103(1):130-135.

(84) Cheanvechai V, Harthun NL, Graham LM, Freischlag JA, Gahtan V. Incidence of peripheral vascular disease in women: is it different from that in men? *J Thorac Cardiovasc Surg* 2004; 127(2):314-317.

(85) Morrell J, Zeymer U, Baumgartner I, Limbourg T, Rother J, Bhatt DL et al. Differences in management and outcomes between male and female patients with atherothrombotic disease: results from the REACH Registry in Europe. *Eur J Cardiovasc Prev Rehabil* 2010.

(86) Palnum KH, Mehnert F, Andersen G, Ingeman A, Krog BR, Bartels PD et al. Medical prophylaxis following hospitalization for ischemic stroke: age- and sex-related differences and relation to mortality. *Cerebrovasc Dis* 2010; 30(6):556-566.

(87) Lee HY, Cooke CE, Robertson TA. Use of secondary prevention drug therapy in patients with acute coronary syndrome after hospital discharge. *J Manag Care Pharm* 2008; 14(3):271-280.

(88) Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA* 2006; 295(2):180-189.

(89) Kotseva K, Wood D, De BG, De BD, Pyorala K, Reiner Z et al. EUROASPIRE III. Management of cardiovascular risk factors in asymptomatic high-risk patients in general practice: cross-sectional survey in 12 European countries. *Eur J Cardiovasc Prev Rehabil* 2010; 17(5):530-540.

(90) Klein-Weigel PF, Gutsche-Petrak B, Wolbergs S, Koning C, Flessenkamper I. Secondary medical prevention in patients with peripheral arterial disease - prescriptions of vascular surgeons and medical doctors (angiologists) in a multidisciplinary vascular centre. *Vasa* 2010; 39(2):145-152.

(91) Fletcher R.H., Fletcher S.W. Clinical epidemiology The essentials. Fourth ed. 2005.

(92) Feringa HH, van Waning VH, Bax JJ, Elhendy A, Boersma E, Schouten O et al. Cardioprotective medication is associated with improved survival in patients with peripheral arterial disease. *J Am Coll Cardiol* 2006; 47(6):1182-1187.

(93) Laustsen J, Jensen LP, Hansen AK. Accuracy of clinical data in a population based vascular registry. *Eur J Vasc Endovasc Surg* 2004; 27(2):216-219.

(94) Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull* 2006; 53(4):441-449.

(95) Frank L. Epidemiology. When an entire country is a cohort. *Science* 2000; 287(5462):2398-2399.

(96) Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999; 46(3):263-268.

(97) Nickelsen TN. [Data validity and coverage in the Danish National Health Registry. A literature review]. *Ugeskr Laeger* 2001; 164(1):33-37.

(98) Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sorensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol* 2011; 11(1):83.

(99) Capella D. Descriptive tools and analysis. *WHO Reg Publ Eur Ser* 1993; 45:55-78.

(100) Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC). *J Vasc Surg* 2000; 31(1 Pt 2):S1-S296.

(101) Austin PC. Propensity-score matching in the cardiovascular surgery literature from 2004 to 2006: a systematic review and suggestions for improvement. *J Thorac Cardiovasc Surg* 2007; 134(5):1128-1135.

(102) Rubin DB. The design versus the analysis of observational studies for causal effects: parallels with the design of randomized trials. *Stat Med* 2007; 26(1):20-36.

(103) Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40(5):373-383.

(104) Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992; 45(6):613-619.

(105) Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004; 159(7):702-706.

(106) Cummings P. Re: "Estimating the relative risk in cohort studies and clinical trials of common outcomes". *Am J Epidemiol* 2004; 159(2):213-215.

(107) Rubin DB. Estimating causal effects from large data sets using propensity scores. *Ann Intern Med* 1997; 127(8 Pt 2):757-763.

(108) Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res* 2011; 46(3):399-424.

(109) Juul S. Epidemiologi og evidens. 2012.

(110) Bismuth J, Klitfod L, Sillesen H. The lack of cardiovascular risk factor management in patients with critical limb ischaemia. *Eur J Vasc Endovasc Surg* 2001; 21(2):143-146.

(111) Eldrup N, Sillesen H. Behandling af perifer karsygdom i almen praksis. *Månedsskrift for parktisk lægegerning* 2011; 82:711-719.

(112) Lalouschek W, Lang W, Greisenegger S, Mullner M. Determination of lipid profiles and use of statins in patients with ischemic stroke or transient ischemic attack. *Stroke* 2003; 34(1):105-110.

(113) Ovbiagele B, Saver JL, Bang H, Chambless LE, Nassief A, Minuk J et al. Statin treatment and adherence to national cholesterol guidelines after ischemic stroke. *Neurology* 2006; 66(8):1164-1170.

(114) Grimshaw JM, Russell IT. Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. *Lancet* 1993; 342(8883):1317-1322.

(115) Coppola G, Romano G, Corrado E, Grisanti RM, Novo S. Peripheral artery disease: potential role of ACE-inhibitor therapy. *Vasc Health Risk Manag* 2008; 4(6):1179-1187.

(116) Narins CR, Zareba W, Moss AJ, Marder VJ, Ridker PM, Krone RJ et al. Relationship between intermittent claudication, inflammation, thrombosis, and recurrent cardiac events among survivors of myocardial infarction. *Arch Intern Med* 2004; 164(4):440-446.

(117) Webb AJ, Rothwell PM. Effect of dose and combination of antihypertensives on interindividual blood pressure variability: a systematic review. *Stroke* 2011; 42(10):2860-2865.

(118) Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. *N Engl J Med* 1998; 339(8):489-497.

(119) Hjalmarson A, Elmfeldt D, Herlitz J, Holmberg S, Malek I, Nyberg G et al. Effect on mortality of metoprolol in acute myocardial infarction. A double-blind randomised trial. *Lancet* 1981; 2(8251):823-827.

Appendix: Overview of the discussed studies related to the use of secondary medical prevention among PAD patients

Abbreviations: CAD, coronary artery disease; CVD, cerebro-vascular disease; CRT, clinical randomized trail

Subject	Author, year, country	N	Study design	Inclusion	Outcome	Findings
Use of secondary medical prevention among PAD patients	Mukherjee D et al. 2002, USA35	66	Follow-up study	PAD patients	Prescriptions rates of secondary medical prevention and clinical outcomes	Anti platelet, ACE inhibitors, beta blocker and statin were prescripted in 77.2%, 35.9%, 2,6% and 50% of the patients, respectively Use of secondary medical prevention was assoiated with a reduction of the composit endpoint of death, MI and stroke (OR 0.02, 95% CI 0.01-0.44)
	Monreal M et al. 2008, Spain77	417	Follow-up Study	Patients with PAD, CAD or CVD	Prescriptions rates of secondary medical prevention and 12 month outcome: MI, Stroke, vascular surgery and cardiovascular death	Anti platelet, beta blocker, calcium antagonist, ACE inhibitor, diuretic and statin 86%, 15%, 27%, 27%, 42% and x62% of the patients, respectively PAD had an increased incidence of major vascular events per 100 patients-years: 17 vs. 7.9 in CAD patients or 8.9 in CVD similar incidence of MI and stroke between the three groups
	Cacoub PP et al. 2009, France73	8322 PAD patients	Follow-up Study	Patients with PAD, CAD or CVD	Prescriptions rates of secondary medical prevention and cardiovascular events	Anti platelet, statin and ACE inhibitors were prescripted in 83.1%, 69.9% and 43.8% of PAD patients in good control of cardiovascular risk factors. Gender- and geographic related differences was shown
	Sigvant B et al. 2009, Sweden25	5,080	Cross-sectional point-prevalence study	Population sample of 60-90 years old patients	Prescriptions rates of secondary medical prevention	Anti platelet and lipid lowering drugs were prescribed in 60.2%, 30.3% of the patients, respectively. Fewer women reported use of secondary medical prevention: OR with male as reference 1.3 lipid lowering drugs, 1.5 anti platelet and 1.3 beta blocker or ACE inhibitor, respectively Geographical related differences were also seen
	Flu HC et al. 2010, The Netherlands76	34,157	Systematic review	24 observa-tional studies. Symptomatic as well as asymptomatic AD patients.	Prescriptions rates of secondary medical prevention	Antiplatelet agents, heart rate lowering agents, blood pressure lowering agents and lipid lowering agents were prescribed in 63%, 34%, 46% and 45% of the patients, respectively
	Mukherjee D et al. 2002, USA35	66	Follow-up study	PAD patients	Prescriptions rates of secondary medical prevention and clinical outcomes	Anti platelet, ACE inhibitors, beta blocker and statin were prescripted in 77.2%, 35.9%, 42,6% and 50% of the patients, respectively Use of secondary medical prevention was associated with a reduction of the composit endpoint of death, MI and stroke (OR 0.02, 95% CI 0.01-0.44)

Appendix: Overview of the discussed studies related to the use of secondary medical prevention among PAD patients

Abbreviations: CAD, coronary artery disease; CVD, cerebro-vascular disease; CRT, clinical randomized trail

Subject	Author, year, country	N	Study design	Inclusion	Outcome	Findings
Use of secondary medical prevention among PAD patients	Klein-Weigel PF et al. 2010, Germany90	264	Cross sectional study	Symptomatic PAD patients undergoing vascular	Prescriptions rates of secondary medical prevention	Beta blocker, ACE inhibitors, ACII, statin, aspirin, clopidogrel and diuretic were prescripted in 38.6%, 53.8%, 71.2%, 90.5%, 6.9%, 6.7% and 39.0% of the patients, respectively
	Müller-Bühl U et al. 2011, Germany78	479 cases 958 controls	Population based case control study	Symptomatic PAD patients compared to patients with CAD	Prescriptions rates of secondary medical prevention	Symptomatic PAD patients were pre scribed less secondary medical prevention than patients with other cardio vascular diseases. Cardiac agents (21%vesues 37%), beta blockers (50.1% versus 66.2%) and lipid lowering agents (50.3% versus 55.9%)
	Coveney AP et al. 2011, Ireland74	159	Follow-up study	PAD patients	Prescriptions rates of secondary medical prevention	Beta blocker, ACE inhibitors, ATII, statin, aspirin, clopidogrel and wafarin were pre scribed in 43.8%, 43.8%, 7.2%, 86.1%, 59.4%, 6.7% and 7.8% of the patients , respectively
Geographical related differences in the use of secondary medical prevention	Bhatt DL et al. 2006, USA88	8,273 PAD patients	Follow-up study	Patients with PAD, CAD and CVD	Prevalence of cardiovascular morbidity and prescriptions rates of secondary medical prevention	Geographical related differences were seen. PAD patients were prescribed less secondary medical prevention patients with other cardio vascular diseases
	Kotseva K et al. UK, 2010[89]	4,366	Follow-up study	Asympto-matic patients just starting-up on secondary medi-cal prevention	Prevalence of cardiovascu-lar morbidity and prescrip-tions rates of secondary medical prevention	Geographical related differences were seen. Targets defined in guidelines was not achieved

Appendix: Overview of the discussed studies related to the efficacy and effectiveness of ACE inhibitor and beta blocker use among PAD patients

Abbreviations: CAD, coronary artery disease; CVD, cerebro-vascular disease; CRT, clinical randomized trail

Subject	Author, year, country	N	Study design	Inclusion	Outcome	Findings
ACE inhibitor use among PAD patients	Ostergren J et al. 2004, Sweden	1725 PAD patients	RCT	Patients with PAD, CAD or CVD	All cause mortality, MI, stroke, and revascularisation	For patients with ABI 0.9-0.6 the RR for primary outcome was 0.72 (95% CI 0.56-0.92), non users (21.6%) compared to Ramipril users (15.7)
	Feringa HH et al. 2006, The Nederlands	1067	Follow-up	Patients with PAD	All cause mortality and associa-tion with the use of secondary medical prevention	Following adjustment: Statin (HR 0.46 95% CI 0.36-0.58), beta blockers (HR 0.68, 95% CI 0.58-0.80), aspirins(HR 0.72 95% CI 0.61-0.84) ACE (HR 0.80 95% 0.96-0.94) were associated with a reduced risk of long term mortality
	Lane DA et al. 2009, UK		Cochran review	RCT of anti hyperten-sive treatment against placebo	Mortality, cardio-vascular events, amputation and progress of PAD and association with the use of antihypertensive treatment	Ramipril reduce the number of cardiovascular events (OR 0.72 95% CI 0.58-0.91). Evidence on various anti hypertensive drugs with PAD is poor
Beta blocker user among PAD patients	Paravastu SCV et al. 2009, UK	119	Review	RCT comparing beta blockers to placebo	Max walking distance and calf blood flow. Cardiovascular morbidity and mortality	Non of the trails showed worsening effect for beta blocker use either in the primary endpoint nor the secondary outcomes