

Cardiovascular Disease and the Use of Swedish Health Care  
Registries and Electronic Medical Data From Primary Care:  
Disease Reality, Risk Factors, Comparative Effectiveness and  
Outcomes

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## 2 ABBREVIATIONS

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CVD	Cardiovascular disease
RCT	Randomized controlled trial
RWD	Real world data
RWE	Real world evidence
PASS	Post-authorisation safety studies
NPR	The National Patient Register
DRG	Diagnosis related groups
SPDR	The Swedish Prescribed Drug Register
EMR	Electronic medical record
PAD	Peripheral artery disease
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
MACE	Major adverse cardiovascular events
HDR	Dutch Hospital Discharge Register
NHI	The National Health Insurance
ACEi	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin receptor blocker
COPD	Chronic obstructive pulmonary disease
CXP	Pygargus Customized eXtraction Program
CPRD	Clinical Practice Research Datalink
HR	Hazard ratio
CI	Confidence intervals
TG	Plasma triglycerides
GP	General practitioner
THIN	The Health Improvement Network
HDR	Dutch Hospital Discharge Register
HES	Hospital Episode Statistics
NHS	National Health Service
NHI	The National Health Insurance program
DAG	Directed acyclic graph
PS	Propensity score
TASTE	Thrombus Aspiration in ST- Elevation Myocardial Infarction in Scandinavia
PCI	Percutaneous coronary intervention
SCAAR	Swedish Coronary Angiography and Angioplasty Registry

### 3 ACKNOWLEDGEMENTS

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I had the privilege of working with highly inspiring, skilled and good co-authors in all three publications. The “pioneer” period, when the concept of combining national register data with data from primary care medical journals was developed for the hypertension and statin studies, was especially interesting since everything was new (at least for me) and methodology and organization for these projects had to be developed from scratch. I was so lucky that I met Bo Lindman in the beginning, a man with a visionary mindset for developing new use of real life data and with the right contacts. Without him I am not sure this had worked out so well.

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## 4 INTRODUCTION

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### 4.1 CARDIOVASCULAR DRUG DEVELOPMENT AND REAL WORLD DATA

Cardiovascular disease (CVD) is the number one cause of death globally. More people die annually due to CVD than from any other cause, with an estimated 17.5 million CVD related deaths in 2012, representing 31% of all deaths globally (1). Of these, an estimated 7.4 million were due to coronary heart disease and 6.7 million were due to stroke (1).

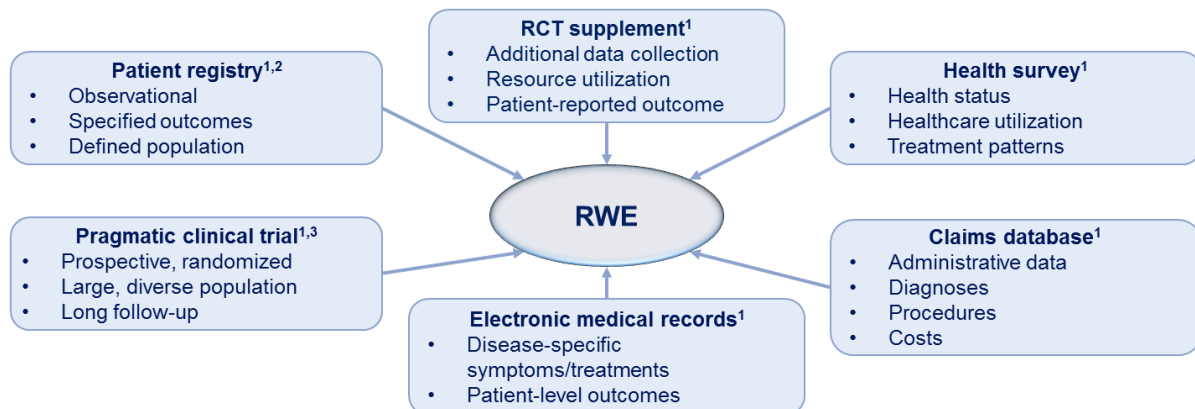
Globally, death due to CVD increased by 41% between the years 1990 and 2013, despite a 39% decrease in age-specific death rates (2). Still, a reduction in CVD related deaths has been observed during the recent years in high-income countries. This reduction is likely due to the combined effect of less exposure to tobacco smoking, changes in diet, and improved treatment by increased use of evidence-based drug therapies, for example blood pressure lowering drugs, statins, platelet inhibitors, and anticoagulants for both cardiovascular risk factors and cardiovascular disease (2).

However, despite this, there is still a global overall increase in the prevalence of cardiovascular disease, even in high-income countries, and cardiovascular disease is still one of the major reasons for death and reduced health globally, and continued need for development of new effective and safe cardiovascular drugs is present.

In the development of new drug therapies, randomized controlled trials (RCTs) are from a methodology perspective considered to be the gold standard (3). However, in the development phase of a drug, there are several research questions might be more comprehensively studied using other research methods than randomised controlled trial design. In addition to this, there is a recognized and increasing demand from regulatory authorities and payers for additional data from real-life treatment settings to complement and support the results from RCTs. Accordingly, there is an increased focus within the pharma industry of the importance of Real-World Data (RWD) (4).

RWD are collected from sources outside of traditional (randomized) clinical trials. These sources may include large trials, or pragmatic clinical trials, prospective observational or register studies, retrospective database studies, case reports, administrative and healthcare claims, electronic health records, data obtained as part of a public health investigation or routine public health surveillance, and registries (e.g., device, procedural, or disease registries) (Figure 1) (5). Real-World Evidence (RWE) is used to refer to the product of aggregation and analysis of RWD (5).

#### 4.1.1 Sources of RWE



1. International Society for Pharmacoeconomics and Outcomes Research. ISPOR Using 'Real World' Data Task Force. Draft Report. 2006. Available from: [www.ispor.org/workpaper/RWD\\_TF/RWTFDraftReport.pdf](http://www.ispor.org/workpaper/RWD_TF/RWTFDraftReport.pdf) (Accessed 04 September 2017)

2. Gliklich, Dreyer, editors. Registries for evaluating patient outcomes: a user's guide. 2nd edn. Rockville: Agency for Healthcare Research and Quality, 2010

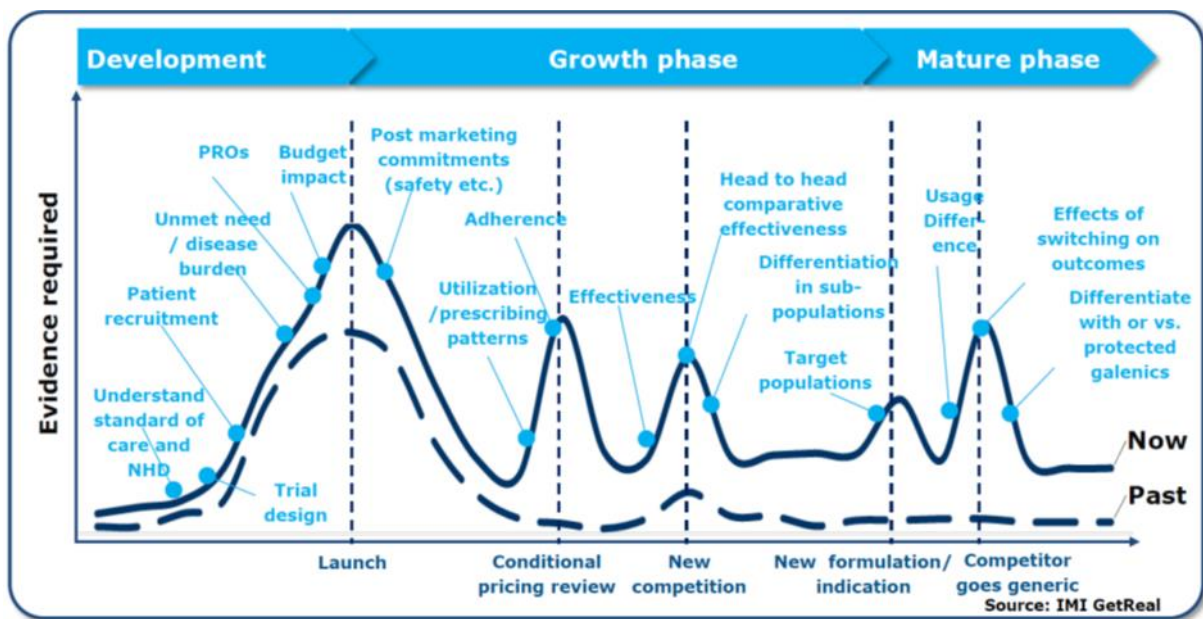
3. Tunis et al. JAMA 2003;290:1624–32 RCT, randomized controlled trial; RWE, real-world evidence

Historically, from a pharma industry development perspective, RWD has primarily an important role in post-marketing drug safety surveillance, where register data with large numbers of unselected patients with generally long follow up time are utilized to study the extended safety profile of drugs. These studies can be initiated by the company itself, or be requested by regulatory authorities (post-authorisation safety studies (PASS)). A classical example of this type of studies is the safety follow up programme for acid suppressive drugs and potential increase risk of cancer (6).

However, as mentioned earlier, an increased demand for RWD is also evident from regulatory authorities and payers. The increase need for RWE in the different phases of a drug life cycle was presented by the European Medicine Agency at a meeting in 2016, as illustrated below (Figure 2) (4).



#### 4.1.2 Need of RWE in different phases of a drug life cycle



For regulatory authorities, pre-launch RWE data on prevalence and incidence, current treatment and disease outcome have become an essential part of the documentation package for a new drug application and/or new indications (7-9). Overall, addition of RWE data may allow for a broader understanding of the data from RCTs, e.g. adding information on the estimated overall size of target patient population, and providing a possible assessment of the generalizability of the results from the RCTs caused by selection of study patients and follow-up vs. real-life populations (10). From a health economic perspective, data from real-world studies have become essential in reimbursement dossiers as a part of cost-effectiveness analyses for new drugs and indications or drugs on the market facing potential price reductions (11).

When the drug is available on the market, treatment reality studies provide important information with data on treatment prescription patterns, i.e. is the drug prescribed according to recommendations and reimbursement criteria, patients' persistence to therapy, and monitoring of potential safety signals (12-14).

RWD is also considered to be a valuable data source for example in sample size estimations for planned randomised trials, and the generation of research questions regarding underlying disease patterns to be tested in randomized trials. Another potential and important area of use for RWD is the evaluation of changes in risk predictors, as this might not be possible to study with a randomised study design where randomisation into different follow up groups might not be feasible. Examples for this include changes in body mass index and association with cardiovascular disease risk after being diagnosed with type 2 diabetes (15), and changes in high density lipoprotein cholesterol after initiation of statin therapy (16).

Furthermore, comparative effectiveness studies where one treatment is compared with another relevant treatment in a real-life setting regarding outcome is becoming a major part of the data needed during a drug’s life cycle. These studies allow outcome in larger, unselected patient populations to be described as a complement to RCT outcome studies (Figure 3), or as an alternative to RCT data when RCT outcome data are not available (17-19). Payer authorities in many countries are starting to request comparative effectiveness data and cost data as a part of negotiations for gaining or maintaining reimbursement for drugs.

4.1.3 Real world evidence complements data from randomized controlled trials

	Randomized controlled trials (RCTs)	real-world evidence (RWE)
Objective	Can it work?	Does it work?
Purpose	Gain regulatory approval	Impact real clinical practice
Setting / design	“Ideal” conditions	“Real world” conditions
Intervention	Fixed regimen	Flexible regimen
Compliance	High	Low to high
External validity	Low to medium: homogenous populations	High: heterogenous populations (including “severe” cases)
Internal validity	High: the intervention is the main difference between groups	Low: the intervention may not be the most important difference between groups

Adopted from Taylor and Gordon (2007). Handbook of research methods in abnormal and clinical psychology  
 RWE, real-world evidence; RCT, randomized controlled trial

Based on the importance of RWD for the pharma industry there is a continued increased search for registries and countries where high quality studies of this type can be performed. The typical limitations of RWD register sources include incomplete historical or geographic coverage, restriction to selected patient groups and lack of complete long term follow-up. In addition, insufficient linkage possibilities with other data sources (for example data on socio-economic status) might also reduce the usefulness of data. Furthermore, the quality of register-based research largely depends on the data validity. The requirements of data completeness and validity are even more critical for comparative effectiveness studies, as there is a risk that residual, unmeasured confounding, or confounding by indication may have affect the results. Furthermore, access to data on health care costs, for example what are main cost drivers within a therapeutic area, the cost for treating selected patient groups are critical information that ideally should be directly retrieved from register data.

## 4.2 SWEDISH NATIONAL REGISTER DATA

In the Nordic countries, public-funded general health care for all citizens, combined with a long history of mandatory registration of data with individual-level linkage possibility via the personal identification number, potentiates unique longitudinal full population-based registers studies with multiple data sources covering entire nations (20).

Sweden, as also seen in the other Nordic countries, has some unique national registries for RWD: The National Patient Register (NPR), started in 1964 with complete national coverage since 1987, covering in-patient admission and discharge dates, as well as out-patient visits, with main and secondary diagnoses according to International Classification of Diseases, 10th revision, Clinical Modification (ICD-10-CM codes). A validation of the NPR reported a general high validity of the diagnoses, although some differences were observed between diagnoses (21). Especially within the CV area, many of the most commonly utilized study endpoints, e.g. heart failure, stroke and myocardial infarction were validated and showed comparatively high positive predictive values (22-24). Furthermore, NPR data also include the costs of hospitalization and interventions according to the Diagnosed Related Groups (DRG) classification system (25).

In addition, there are several disease specific quality registries in Sweden, often with nation-wide coverage (26). These registries contain more detailed clinical data for a specific disease area, and one of the most well-known examples within the cardiovascular disease area is the Swedeheart register(27), but comprehensive nationwide registers are present also for stroke (28), heart failure (29) and PAD (30).

The Swedish Prescribed Drug Register (SPDR), with nationwide coverage from 1 July 2005 include data on all drugs dispensed by pharmacies in Sweden. The register contains data on the date of prescription and dispense; substance, brand name, formulation, package, amount and dosage for the dispensed item; age, sex and a where the patient lives; as well as type of prescribing practice (primary care centre or hospital clinic) and the prescriber's profession (31).

The Swedish Cause of Death register (from 1961) reports annual death data by age, sex, cause, place of death, and municipality of residence. Since 2011 the register includes mortality data on all deceased persons who at the time of death was registered in Sweden, no matter if the death occurred within or outside the country (32).

## 4.3 SWEDISH PRIMARY CARE DATA

A patient in Sweden has normally only one general practitioner who follows the patient and is responsible for documenting their examinations in the electronic medical record (EMR). EMRs have

been in use of more than 95% of primary care centres since 2005 (17). The EMRs are continuously updated with external data, i.e. radiologic results, ultrasound examinations, hospital discharge data, and laboratory data (17). In addition, the same disease coding system (ICD-9/10) is used in primary care and hospitals in Sweden, thus allowing easy monitoring of diseases across different care giving levels. One major limitation in Swedish RWD is the access to data from primary care, since there is no public primary care register in place. One feasible method to collect primary data is direct electronic extraction of EMR data directly by different extraction programs (33).

## 5 AIMS OF THE THESIS

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The aim of this PhD thesis is to describe the suitability of Swedish national health care registry data and electronic medical records data from primary care in Sweden in the different phases of cardiovascular drug development and life cycle management:

- 1) To study long-term cardiovascular outcome, health care resource use, and health care costs in patients with peripheral artery disease (Paper I), as an example of a study on current treatment, outcome, resource use and costs of a disease area.
- 2) To study the association between paradoxical HDL cholesterol decrease and risk of major adverse cardiovascular events in patients initiated on statin therapy (Paper II), as an example of evaluation of changes in risk predictors on outcome.
- 3) To study diabetes and CVD risk during angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker treatment in patients with hypertension (Paper III), as an example of a comparative effectiveness study.

Furthermore, the methodological challenges related to different types of RWE studies in different phases of drug development will be illustrated and discussed.

## 6 PUBLICATIONS

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1. Hasvold P, Sigvant B, Kragsterman B, Kristensen T, Falkenberg M, Johansson S, Thuresson M, Nordanstig J. Long-term cardiovascular outcome, use of resources, and healthcare costs in patients with peripheral artery disease: Results from a nationwide Swedish study. *European Heart Journal - Quality of Care and Clinical Outcomes*, qcx028, <https://doi.org/10.1093/ehjqcco/qcx028>
2. Hasvold P, Thuresson M, Sundström J, Hammar N, Kjeldsen SE, Johansson G, Holme I, Bodegård J. Association Between Paradoxical HDL Cholesterol Decrease and Risk of Major Adverse Cardiovascular Events in Patients Initiated on Statin Treatment in a Primary Care Setting. *Clin Drug Investig*. 2016 Mar;36(3):225-33
3. Hasvold LP, Bodegård J, Thuresson M, Stålhammar J, Hammar N, Sundström J, Russell D, Kjeldsen SE. Diabetes and CVD risk during angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker treatment in hypertension: a study of 15,990 patients. *J Hum Hypertens*. 2014 Nov;28(11):663-9

## 7 ETHICAL CONSIDERATIONS

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### Paper I

The study protocol was reviewed and approved by the regional ethics committee of the University of Gothenburg, Sweden (reference number: 649-14). Linkage of data was performed by the Swedish National Board of Health and Welfare. The linked database was managed by the Institute of Medicine at the Sahlgrenska Academy, Gothenburg, Sweden.

### Paper II

The study protocol was reviewed and approved by the regional research ethics committee in Uppsala, Sweden (Reference number 2012/007) and registered at ClinicalTrials.gov (clinical trial identifier NCT01551784). The linked study database is owned and managed by the Department of Public Health and Caring Sciences, Uppsala University, Uppsala (16).

### Paper III

The study protocol was reviewed and approved by the Regional Research Ethics Committee in Uppsala, Sweden and registered with ClinicalTrials.gov, NCT01152567. The study database was owned and managed by the Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden (34).

Data for all papers were analyzed using de-identified data.

## 8 METHODS

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### 8.1 PAPER I

For this observational cohort study, data were extracted from three mandatory Swedish nationwide registries: NPR, SPDR, and the Swedish Cause of Death Register. Individual patient-level data from the registers were linked by the Swedish National Board of Health and Welfare.

All patients with a first time primary or secondary diagnosis of PAD in a hospital setting (as in-patient or out-patient), ICD-10 I70.0 (atherosclerosis of aorta), I70.2 (atherosclerosis of arteries of extremities), or I73.9 (claudicatio intermittens), between 2006 and 2013 were included.

The population was stratified by age and risk profile at index date (discharge from hospital with PAD diagnosis):

- Patients aged < 65 years
- Patients aged 65–75 years
- Patients aged > 75 years

Patients with one or more of the following comorbidities were defined as high-risk CV patients: diabetes mellitus, MI, stroke, heart failure, or chronic renal dysfunction. Patients without these conditions were classified as low risk.

#### 8.1.1 Clinical outcomes

The primary endpoint of major CV events was a composite of hospitalization with a main diagnosis of non-fatal MI (ICD-10: I21), non-fatal IS (ICD-0: I63-I64), or CV death (ICD-10 codes I00–I99). Lower limb revascularization was defined as an open or endovascular procedure, as captured in NPR based on procedure codes.

#### 8.1.2 Resource use

Data on hospitalizations and out-patient care visits were collected from the NPR. The primary diagnosis defined the event type, in those cases where a patient had both a primary and a secondary diagnosis.

Resource use associated with CV disease included hospitalizations, out-patient care visits, and drug use, whereas non-CV related care included all care not related to CV (ICD-10 I). All non-procedural lower limb-related events were included in the category “CV events”. Lower limb procedures included only invasive procedures for treatment of PAD.



Data on dispense, prescribed drugs in terms of substance, formulation, dose, and date of administration were collected from the Prescribed Drug Register. Cardiovascular drugs included drugs in the ATC class C. Non-cardiovascular drugs were defined as all drugs not included in the ATC class C.

### 8.1.3 Health care costs

Each recorded hospitalization and out-patient care visit was assigned a 2015 diagnosis-related group (DRG) weight, which was multiplied by the most recent 2015 cost per weight. In cases of missing DRG codes in the 2015 DRG catalogue, older DRG catalogues were used to apply the correct weight. If DRG codes recorded before 2015 had been stratified into several DRG codes in the 2015 DRG catalogue, a weighted average of these weights was applied. Irrespective of the year in which the DRG code was recorded, all costs were multiplied by the most recent cost per weight.

The daily cost of a drug was calculated by multiplying the average dose by the most recent retail price available.

### 8.1.4 Analysis

Follow-up data were collected from the time of the index diagnosis of PAD until death or the end of follow-up. The frequency and proportion of patients with the primary composite endpoint were assessed and a Kaplan–Meier analysis was performed to estimate the cumulative probability of the primary composite endpoint during study follow-up. If one patient had several events, only the first was used in the survival model.

Resource use was calculated for each year, i.e. one year before initial PAD diagnosis, the year after being diagnosed with PAD (starting from the hospital admission date, or the date recorded for the out-patient visit when the PAD diagnosis was established), and the five years that followed. Patients contributed to a particular year of analysis if they died during the year or had a full year of exposure.

Mean healthcare costs per patient per year were estimated by applying unit costs to the corresponding resource use items. If a patient had both a PAD CV-related diagnosis and a lower limb procedure performed at the same visit, the costs were reported as being lower limb-related.

## 8.2 PAPERS II AND III

### 8.3 PAPER II

#### 8.3.1 Data sources

In this study, data were extracted from three nationwide Swedish nationwide registries: NPR, SPDR, and the Swedish Cause of Death Register.

Data from primary care was collected at 76 primary care centers in Sweden, using a software system called Pygargus XPD (33). The personal identification number for each patient is replaced with a study ID prior to further data processing. The file linking personal identification number and study ID was stored separately by the principal investigator. Data linkage was performed by the Swedish National Board of Health and Welfare.

#### 8.3.2 Patient population

Patients between 18 and 85 years who started first time statin therapy between 2004 and 2009 were eligible for inclusion. Eligible patients had to have HDL-C and LDL-C measurements within 12 months before start of statin treatment, as well as a measurement after 10 days and within 12 months on statin treatment. Excluded patients were; 1) patients with cardiovascular events before the first HDL-C measurement while on statin treatment, 2) patients with history of alcohol abuse and on-going malignancy, 3) patients with an LDL-C lowering of less than 0.5 mmol/l due to insufficient statin effect or indication of low compliance to statin treatment.

The date of first statin dispense was defined as start of statin treatment. The start of the observation period for collecting endpoints was date of first HDL-C measurement on statin treatment. The end of the study observation was 31 December 2011, the end of statin treatment, or death. If a statin treatment gap of more than 90 days was observed, based on available dispensed drug data, the end of statin treatment was defined as calculated days on last available dispensed drug package plus an additional 25% of days based on the last dispensed drug pack size.

Three HDL-C groups were defined based on change in between last HDL-C measurement prior statin treatment and first HDL-C measurement on at least 14 days of statin treatment: HDL-C decrease: more than 0.1 mmol/L and HDL-C unchanged group:  $\pm 0.1$  mmol/L. To explore the effect of HDL-C increase, a group with more than 0.1 mmol/L increase in HDL-C was defined.

The analysis was performed in two patient samples; the matched sample, which included HDL-C decrease and unchanged HDL-C patients who fulfilled the inclusion and exclusion criteria and who could be propensity score matched for baseline characteristics regarding propensity of HDL-C

decrease. The unmatched population used for sub group analyses comprised all patients who fulfilled the inclusion and exclusion criteria.

### 8.3.3 Outcome

The major adverse cardiovascular event (MACE) endpoint was a composite of hospitalization for a primary diagnosis for myocardial infarction (ICD-10, I21), unstable angina pectoris (ICD-10, I20.0), ischaemic stroke (ICD-10, I63), or cardiovascular death (all primary causes of death diagnosed with ICD-10 codes I00–I99).

### 8.3.4 Analysis

Logistic regression models were included to estimate the propensity scores between the decreased and unchanged HDL-C groups, with the HDL-C decrease as the response variable and the following covariates: age, gender, baseline HDL-C, baseline LDL-C, LDL-C change on statin treatment, antihypertensive therapy, diagnosis of diabetes, heart failure, hypertension, angina pectoris, peripheral artery disease (PAD), and stroke.

The propensity scores were matched pairwise, with exact matching for prior myocardial infarction and use of calipers of width equal to 0.1 of the standard deviation of the propensity score. The primary endpoint was analyzed by a Cox proportional hazards model, using a grouped jack-knife estimation of the variance to take the correlation within pairs into account.

The association between HDL-C change and the primary endpoint in the decreased and increased HDL-C groups was studied in the following sub groups: gender (men/women), primary/secondary prevention, with/without diabetes, and in patients above 75 years of age versus younger patients. In the sub group analyses, Cox regression with adjustment for age, gender, baseline HDL-C, baseline LDL-C, LDL-C change on statin treatment, antihypertensive therapy, diagnosis of diabetes, heart failure, hypertension, angina pectoris, PAD, and stroke was used.

## 8.4 PAPER III

### 8.4.1 Data sources

In this study, data were extracted from three nationwide Swedish nationwide registries: NPR, Swedish Cause of Death Register and Statistics Sweden (data on socio-economic status (educational level)).

Data on all patients prescribed either ACEi or ARB at 71 primary care centers from 1 January 1999 to 31 December 2007 were extracted and processed the same way as data in paper II.

Candesartan, being one of the two most frequently prescribed ARB in Sweden was chosen to represent the ARBs in this comparison in order to reduce potential confounding. Enalapril was chosen to represent the ACEis because of identical indications to candesartan and being the most frequently prescribed ACEi in Sweden (75% of patients receiving ACEis).

#### 8.4.2 Study population

Patients aged 18 years or older, who for the first time were prescribed either enalapril or candesartan, with or without a fixed combination with hydrochlorothiazide, were eligible for the study. The first prescription of the study drug within the study period was defined as the start of the study. Exclusion criteria were a recorded diagnose of CVD, diabetes, chronic kidney disease or malignancy. Patients who were prescribed vitamin K antagonists, clopidogrel, acetylic salicylic acid, digitalis glycosides, aldosterone antagonists, loop diuretics, nitrates or anti-diabetes drugs within 15 months prior to study start were considered to have potential CVD or diabetes and were excluded.

Data on age, gender, blood pressure values and body mass index (BMI), laboratory/blood samples, diagnoses, number of visits and prescribed drugs were extracted from the primary care journals. The baseline for the blood pressure value was calculated as the mean of the last three measurements during the time period 15 months before until 14 days after the start of enalapril or candesartan treatment. Blood pressure at 6 months was calculated as the mean of measurements 2 weeks to 6 months after study start. From 12 months and onwards, 6-monthly blood pressures were calculated as the mean of measurements from 6 months before to 6 months after the specific time point.

#### 8.4.3 Follow-Up and Outcomes

Patients were eligible for analysis while they remained on study drug treatment. The observation period ended on the date when the patient died, discontinued the study drug treatment, started a new RAS inhibiting drug, or on the 31 December 2007.

The criteria for the diagnosis of diabetes in Sweden is normally based on elevated plasma glucose values (>7.0 mmol/L) and/or a positive oral glucose tolerance test. The endpoint for diabetes was a recorded primary care or hospital discharge diagnosis of type 2 diabetes (ICD-9 code 250, ICD-10 codes E10-E14) and/or prescription of a drug within the ATC system class A10. This endpoint for diabetes diagnosis have been validated in other studies. The end-point for assessing CVD consisted of a recorded diagnosis of all non-fatal and fatal CVD (myocardial infarction, unstable angina, chronic ischemic heart disease, peripheral artery disease, heart failure, cardiac arrhythmias and stroke) as defined by ICD codes.

Time to event end-points were analyzed using Cox proportional hazards regression models. If one patient had several endpoints, only the first was used in the survival model. Time to diabetes or CVD was analyzed separately.

#### 8.4.4 Selection of Covariates for the Primary Analysis

Patients with a history of renal disease, CVD and/or diabetes were excluded from this study. Age, gender, elevated blood glucose, overweight and low socioeconomic status are known risk factors for diabetes, and high cholesterol and hypertension are additionally known risk factors for CVD. All included patients had hypertension and there was no difference between the two treatment groups regarding baseline lipid values and statin use. The socioeconomic status is associated with smoking pattern, overweight and physical activity, thus a risk factor for diabetes and CVD. The treatment patterns (diagnoses, treatment targets) may change over time, and the primary analysis was therefore adjusted for age and gender at baseline, socioeconomic status and year of study start.

The primary analysis was supported by sensitivity analyses where additional covariates with incomplete coverage at baseline were included and analyses with exclusion of endpoints recorded within a specific time-frame after study start.

#### 8.4.5 Sensitivity Analyses Diabetes

For diabetes, additional sensitivity analyses were performed where baseline HbA1c, blood glucose and BMI were included as additional covariates. The diagnosis of diabetes within 6 and 12 months after the start of study were also excluded in extra analyses for diabetes and CVD.

#### 8.4.6 Sensitivity Analyses for Diabetes and CVD

The propensity scores for receiving either enalapril or candesartan were calculated using a logistic regression model in which the dependent variable was use of enalapril or candesartan. Independent covariates included in the model were gender, age, year of study start, systolic blood pressure, total cholesterol, blood glucose, socio-economic status, beta blockers, statins, calcium antagonists, and thiazides. Blood glucose was selected as covariate for laboratory samples related to diabetes, since the elevated blood glucose is the main diagnostic criterion for diabetes in Sweden. The resulting propensity scores were matched pair wise using calipers of width equal to 0.2 of the standard deviation of the propensity score using the matching package in R. Risk of new onset diabetes and CVD were calculated using a Cox proportional hazards model stratified by the matched pairs.

For both end-points, the same model for adjusted Cox regression with multiple imputation of systolic blood pressure as additional covariate was applied. The potential effect of variation in proportion of

included patients per year in the two cohorts was also studied by analyzing the cohorts of patients included before and after 2005 separately.

## 9 RESULTS AND DISCUSSION

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### 9.1 NATIONAL REGISTER DATA (PAPER I)

The paper 1 “Long-term cardiovascular outcome, use of resources, and healthcare costs in patients with peripheral artery disease: Results from a nationwide Swedish study” is an example of the opportunities Swedish national registers data can provide for studies with the aim of describing size of patient populations, outcomes, resource use, and health care costs.

Paper I included all patients newly diagnosed with PAD in the Swedish National Patient Register between 2006-2014, and subsequently linked to cause of death- and prescribed drug registers. The mean per-patient annual healthcare costs (reported in Euros [€]) (hospitalisations and out-patient visits) were divided into cardiovascular (CV), lower limb and non-CV related cost. Results were stratified by high CV risk, patient with diabetes mellitus, MI, stroke, heart failure, or chronic renal dysfunction, and low CV risk (i.e. without any of the mentioned diseases).

Overall, 141,266 patients with a diagnosis of PAD were identified, of which 66,189 had their first PAD diagnosis established during the observation period and could be included in the study. PAD was mainly diagnosed at hospital out-patient visits (71%), and was the main reason for hospital contact for 77% of the patients. Mean length of follow-up was 2.8 years, with a maximum of 8 years, resulting in a total of 184,614 patient-years of follow-up. Baseline characteristics of the PAD study population are presented in the table below.

### 9.1.1 Baseline characteristics of patients diagnosed with PAD

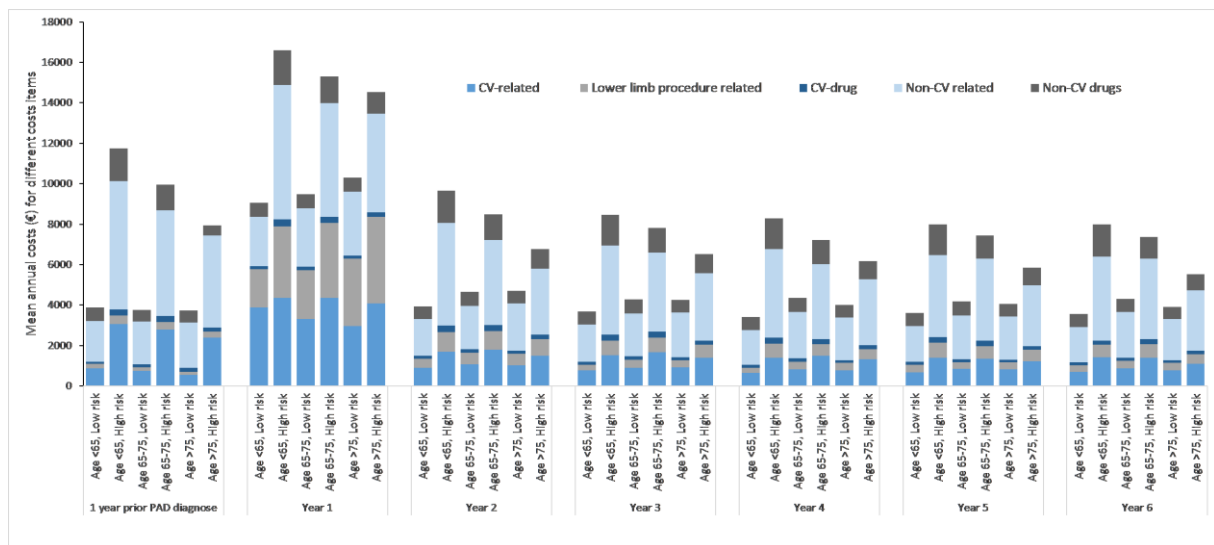
	Age <65 High-risk n=5,050	Age <65 Low-risk n=5,752	Age 65-75 High-risk n=10,733	Age 65-75 Low-risk n=9,908	Age 75+ High-risk n=21,068	Age 75+ Low-risk n=13,678	Total n=66,189
Age (SD)	59.5 (3.8)	59.3 (3.9)	70.4 (3.1)	70.1 (3.1)	84.0 (5.2)	83.4 (5.3)	75.6 (10.3)
Gender (Female)	1,567 (31.0)	2,510 (43.6)	3,719 (34.7)	4,914 (49.6)	10,595 (50.3)	8,297 (60.7)	31,602 (47.7)
Aorta aneurysm	163 (3.2)	258 (4.5)	712 (6.6)	708 (7.1)	951 (4.5)	629 (4.6)	3,421 (5.2)
Diabetes	3,594 (71.2)	0 (0.0)	6,977 (65.0)	0 (0.0)	9,840 (46.7)	0 (0.0)	20,411 (30.8)
Hypertension	4,284 (84.8)	2,708 (47.1)	9,585 (89.3)	6,326 (63.8)	18,086 (85.8)	9,397 (68.7)	50,386 (76.1)
Myocardial infarction	1,409 (27.9)	0 (0.0)	3,189 (29.7)	0 (0.0)	6,391 (30.3)	0 (0.0)	10,989 (16.6)
Angina pectoris	1,553 (30.8)	474 (8.2)	3,700 (34.5)	1,129 (11.4)	6,754 (32.1)	1,913 (14.0)	15,523 (23.5)
Ischemic stroke	794 (15.7)	0 (0.0)	2,433 (22.7)	0 (0.0)	6,040 (28.7)	0 (0.0)	9,267 (14.0)
Heart failure	1,141 (22.6)	0 (0.0)	3,303 (30.8)	0 (0.0)	10,464 (49.7)	0 (0.0)	14,908 (22.5)
Atrial fibrillation	636 (12.6)	205 (3.6)	2,495 (23.2)	808 (8.2)	8,823 (41.9)	2,256 (16.5)	15,223 (23.0)
Major organ specific bleedings	433 (8.6)	231 (4.0)	1,088 (10.1)	553 (5.6)	2,941 (14.0)	1,161 (8.5)	6,407 (9.7)
Chronic renal insufficiency	548 (10.9)	0 (0.0)	862 (8.0)	0 (0.0)	951 (4.5)	0 (0.0)	2,361 (3.6)
Chronic obstructive pulmonary disease	428 (8.5)	325 (5.7)	1,448 (13.5)	961 (9.7)	2,310 (11.0)	1,027 (7.5)	6,499 (9.8)
Cancer	449 (8.9)	563 (9.8)	1,822 (17.0)	1,750 (17.7)	4,883 (23.2)	3,013 (22.0)	12,480 (18.9)
Anti-platelets	3,711 (73.5)	3,689 (64.1)	7,974 (74.3)	6,767 (68.3)	14,893 (70.7)	8,677 (63.4)	45,711 (69.1)
Clopidogrel	731 (14.5)	333 (5.8)	1,463 (13.6)	638 (6.4)	2,166 (10.3)	769 (5.6)	6,100 (9.2)
Low dose aspirin	3,525 (69.8)	3,564 (62.0)	7,455 (69.5)	6,453 (65.1)	13,856 (65.8)	8,233 (60.2)	43,086 (65.1)
Warfarin	479 (9.5)	243 (4.2)	1,694 (15.8)	608 (6.1)	3,843 (18.2)	1,169 (8.5)	8,036 (12.1)
Statins	3,793 (75.1)	3,383 (58.8)	7,816 (72.8)	6,168 (62.3)	8,985 (42.6)	5,301 (38.8)	35,446 (53.6)
Anti-hypertensives	4,429 (87.7)	3,095 (53.8)	9,938 (92.6)	7,007 (70.7)	19,842 (94.2)	10,908 (79.7)	55,219 (83.4)
Anti-diabetics	3,263 (64.6)	17 (0.3)	6,159 (57.4)	19 (0.2)	7,915 (37.6)	20 (0.1)	17,393 (26.3)
Analgesics	2,478 (49.1)	2,124 (36.9)	5,742 (53.5)	3,957 (39.9)	14,851 (70.5)	8,017 (58.6)	37,169 (56.2)

Adapted from Hasvold P, Sigvant B, Kragsterman B, Kristensen T, Falkenberg M, Johansson S, Thureson M, Nordanstig J. Long-term cardiovascular outcome, use of resources, and healthcare costs in patients with peripheral artery disease: Results from a nationwide Swedish study. *European Heart Journal - Quality of Care and Clinical Outcomes*, qcx028, <https://doi.org/10.1093/ehjqcco/qcx028> (35)

The overall 1-year cumulative incidence rates of the primary composite CV endpoint (myocardial infarction, stroke, or CV death) and all-cause death were 16.6% and 21.1%, respectively. Mean total healthcare costs per patient were €6,577 during the year prior to the PAD diagnosis, of which 26% was CV-related (€1,710). First year after PAD diagnosis, healthcare costs were €12,549 per patient (?), of which €3,824 (30%) was CV-related and €3,201 (26%) lower limb related. High-risk CV patients had higher annual total healthcare- and CV related costs during follow-up, compared to low risk CV patients (€7,439 and €1,442 versus €4,063 and €838, respectively). Annual lower limb procedure costs were €728 in the PAD population, with lower limb re-vascularizations as key cost driver (€474). The presence of additional risk factors, other than age, were the main drivers for both CV-related and non-CV-related costs, see figure below.



### 9.1.2 Annual costs per patient prior to and after peripheral artery disease (PAD), by cost category, age, and risk



Cardiovascular (CV)-related: includes all ICD-10 CV “I” diagnoses except PAD-related costs in combination with lower limb procedures. If a PAD patient had a hospitalization with a PAD diagnosis ‘I’ and a lower limb procedure, then the cost for this visit is reported as being lower limb procedure-related. Non-CV-related: all costs except costs related to CV (ICD-10 “I”).

Adapted from Hasvold P, Sigvant B, Kragsterman B, Kristensen T, Falkenberg M, Johansson S, Thuresson M, Nordanstig J. Long-term cardiovascular outcome, use of resources, and healthcare costs in patients with peripheral artery disease: Results from a nationwide Swedish study. *European Heart Journal - Quality of Care and Clinical Outcomes*, qcx028, <https://doi.org/10.1093/ehjqcco/qcx028> (35)

Compared to patients with MI, the total annual CV-related costs, excluding lower limb procedure costs, were higher for PAD patients during long-term follow-up, with a mean of €1,945 per patient as opposed to approximately €1,700-1,800 per patient; an effect of the progressive, chronic nature of PAD. Also, lower limb procedure-related costs were initially high, and remained so during the subsequent follow-up of these patients. Although the PAD population has a both well-recognized and high CV risk, the major proportion of hospitalization costs for PAD patients are not related to CV disease (29). (35).

The present study had some limitations. First, we did not have access to data describing the extent and severity of PAD, which may have had an impact on the treatment cost.

However, this access to register data combining the full population perspective, complete follow-up of patients over time, with validated endpoints (including cause of death) in combination with actual costs data is rather unique for the Nordic countries.

## 9.2 SWEDISH NATIONAL REGISTER DATA VS OTHER DATA SOURCES

In relation to Paper I and the utilization of Swedish national register data, its uniqueness can further be illustrated by the paper by Rapsomaniki et al 2016, where long-term cardiovascular outcome of post-myocardial infarction patients was compared between US, UK, France and (36). Here, Sweden was used as reference country regarding outcome, due to the full population coverage, with complete follow up and validated outcomes, whereas patients in the other countries were included on various criteria like specific health insurance coverage, age, or follow up by selected primary care physicians.

Another major advantage with Swedish NPR data, is that DRG codes are specified and available for each visit, making generation of health care costs data from a hospital care setting easily processed. In the Nordic, besides Sweden these data are also easily accessible in Norway, but not in Denmark. These data are the same as used by authorities for estimating resource use and cost settings for different types of hospitalizations and interventions.

Furthermore, the Swedish NPR also contains a substantial number of recorded procedural codes in addition to those classified as surgical (surgery performed in an operating room), for example detailed data on angiography or echocardiography procedures (37). Since reporting of these procedure codes are a mandatory part of the resource funding system for hospitals (as a major part of the DRG calculation), it is likely that these data are rather complete. However, the procedural data are not often yet extensively included in studies and might be additional valuable variables to include in future studies.

Several other registers sources/countries outside Sweden and the Nordics can provide partly similar data as Sweden. However, often is the full population perspective missing, since data for only selected patient groups are available, or the DRG data are missing, and in other cases, is the unique personal identification number missing, making linking to other data sources difficult.

One example is the Netherlands, where the Dutch Hospital Discharge Register (HDR), started in 1963, contains similar diagnosis data as NPR in Sweden, however lacking data on out-patients visits and cost data. Since a complete patient identifying information (personal identification number) is missing, linkage approach to other data sources is potentially challenging (38, 39).

A few other countries also present as potential options. In the UK, the United Kingdom's Clinical Practice Research Datalink has recorded comprehensive information on both diagnoses, clinical data, and drug therapy prescribed in selected primary centers since 1987. This data base covers 9% of the UK population and is broadly representative of the wider population (40). However, hospital data is only available for a subset of patients, thus full population perspective is absent (40). Another

alternative in England is the Hospital Episode Statistics (HES), a data warehouse containing details of all admissions to National Health Service (NHS) hospitals in UK (41). However, a limitation with these data, is the linkage possibility to other data sources, for example, it is not possible to link with data on prescriptions. Also, the health improvement network (THIN) primary care database, containing records of approximately 5.7% of UK population, which can be linked to HES data, is an alternative (42, 43).

In the United States, the access to register data is restricted to certain age groups (44), income groups, professions, or members of private health insurance schemes (45), often without the possibility of linkage with other data, and with only limited historical data or long-term follow-up data (20).

Taiwan has some unique register data opportunities. The National Health Insurance (NHI) program is a national, single, and mandatory health insurance program since 1995, which by 2014 covered 99.9% of Taiwan's population (46). These register data include patient identifications, dates of the ambulatory or inpatient care provided, disease classification codes (ICD-9-CM codes), physician IDs, physician specialties, hospital IDs, surgical and non-surgical procedures performed, and the drug therapy prescribed. The advantage with these registers is that they cover both primary and secondary care, include relevant clinical data (e.g. laboratory data, weight, blood pressure), and are also linkable with other data sources on for example health care costs and socioeconomic status of the patients. Data from this register has been used in numerous studies (46).

When critically reviewing, the options provided by the Swedish registers of course these data have also several limitations that needs to be taken into consideration when utilizing them. A major limitation with Swedish national register data is that data on drug therapy given in an in-hospital setting is not available. Especially in disease areas where most of the drug therapy is given during hospital stays, for example cancer, this a significant limitation if the aim is to study effects of drug therapy. However, within many therapy areas, and especially within the CV area, in-hospital drug therapy data for the disease are sometimes included in the nation-wide disease specific quality registers which then potentially can be utilized to cover that aspect (27, 29).

Another limitation is the potential low number of patients due to the low number of inhabitants in Sweden. For example, for safety studies, where the aim is to describe rare safety signals associated with different treatments, or in comparative effectiveness studies where number of patients treated is not enough for showing differences between treatment groups. However, there is an increasing cooperation between Scandinavian countries regarding register data, and since the health care

system and data are similar in Denmark and Norway, thus there is a potential to increase the accessible population size by doing pan Nordic studies (47, 48).

### 9.3 PRIMARY CARE DATA FROM SWEDEN (PAPER II AND III) IN COMBINATION WITH NATIONAL REGISTER DATA

Primary care centers have a central function in the health care system in Sweden, commonly being the first and main point-of-contact with the health care system, and having a gatekeeper function for referrals to secondary care. The access to primary care data gives for example access to important clinical data on blood pressure, weight, BMI, laboratory samples/results. Furthermore, as long-term caregiving, for often complicated chronic diseases such as COPD, atrial fibrillation, and type-2 diabetes, is provided in primary care, access also provides the possibility of having a complete overview of the care giving pattern, e.g. how often the patient is seen by a primary care physician or nurse etc. This information is vital in studies involving diseases where a major part of the care giving is provided in primary care (17, 18, 34).

Papers II and III, on HDL and ARB/ACE, are both examples of the use of national register data linked to Swedish EMR data, from approximately 7% of the total number of primary care centers in Sweden, and thereby covering a significant part of the Swedish population.

#### 9.3.1 Paper II

In paper II, data for eligible patients, aged 18-85 years and initiated first time statin treatment between 2004 and 2009, were extracted from primary care electronic medical records at 76 primary care centers. This primary care data were linked with data from the NPR and cause of death register, and were grouped according to HDL-C change: decreased  $\geq 0.1$  mmol/L, unchanged  $\pm 0.1$  mmol/L or  $\geq 0.1$  mmol/L increased.

To evaluate the association between decrease in HDL-C and risk of MACE, a sample of propensity score-matched patients from the decreased and unchanged groups was created, using the latter group as reference. Cox proportional hazards models were used to estimate relative risks.

The baseline mean age was 62.7 years (range 19–85 years) and mean HDL-C was 1.48 mmol/L. The majority of patients (96%) were initiated on simvastatin, with a mean dose of 20 mg/day. Of these patients, 20% had a decrease in HDL-C during the observation period, 58% were unchanged, and 22% had an increase. The patient group with a decrease in HDL-C comprised more women, had a higher HDL-C at baseline (1.69 mmol/L), less diabetes, compared with the unchanged HDL-C group. The groups were similar regarding comorbid cardiovascular diagnoses; myocardial infarction, angina pectoris, PAD, stroke or heart failure (Table 2).

The decreased and unchanged HDL-C groups showed a large degree of propensity score overlap (71%), indicating that these groups were similar prior to the start of statin treatment. After matching, the decreased and unchanged HDL-C groups had similar baseline characteristics and LDL-C changes, with the exception of a higher simvastatin dose and lower triglyceride level in the decreased HDL-C group (Table 2). In paper II, data for patients who were eligible for inclusion if they were aged 18-85 years and started first time statin therapy between 2004 and 2009, were extracted from primary medical records at 76 primary care centers. Primary care data was linked with data from the NPR and cause of death register, and were grouped according to HDL-C change: decreased  $\geq 0.1$  mmol/L, unchanged  $\pm 0.1$  mmol/L or  $\geq 0.1$  mmol/L increased.

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### 9.3.2 Baseline characteristics for patients with a decrease in HDL-C ( $\geq 0.1$ mmol/L), an increase in HDL-C ( $\geq 0.1$ mmol/L), or no change in HDL-C ( $\pm 0.1$ mmol/L) (unmatched and propensity score-matched populations)

Variable	Unmatched population			Propensity score-matched population		
	Decreased (n = 3068)	Unchanged (n = 8919)	Increased (n = 3370)	Decreased (n = 2975)	Unchanged (n = 2975)	p value <sup>a</sup>
Women, n (%)	1872 (61.0)	4840 (54.3)	1997 (59.3)	1803 (60.6)	1798 (60.4)	0.92
Age (years)	62.3 (10.2)	62.6 (10.2)	63.0 (9.8)	62.2 (10.1)	62.3 (10.2)	0.64
Simvastatin, n (%)	2925 (95.3)	8510 (95.4)	3244 (96.3)	2835 (95.3)	2823 (94.9)	0.09
Dose (mg)	20.8 (9.7)	19.7 (8.7)	20.2 (8.8)	20.8 (9.7)	19.7 (8.4)	<0.01
Hospitalisations, number/year prior to statin start	0.2 (0.6)	0.2 (0.6)	0.19 (0.6)	0.2 (0.6)	0.2 (0.6)	0.16
Systolic blood pressure (mmHg)	144.6 (19.8)	143.6 (18.6)	144.0 (18.9)	144.6 (19.8)	143.3 (19.0)	0.02
Diastolic blood pressure (mmHg)	82.6 (10.4)	82.0 (10.1)	82.0 (10.4)	82.7 (10.4)	81.9 (10.2)	0.01
Body mass index (kg/cm <sup>2</sup> )	28.6 (5.0)	29.4 (5.0)	28.8 (4.9)	28.7 (5.0)	28.6 (5.2)	0.67
HbA1c (%)	5.5 (1.3)	5.7 (1.3)	5.64 (1.4)	5.6 (1.3)	5.6 (1.4)	0.77
HDL-C (mol/L)	1.69 (0.47)	1.41 (0.40)	1.44 (0.42)	1.66 (0.43)	1.66 (0.45)	0.95
LDL-C (mmol/L)	4.53 (1.00)	4.45 (0.95)	4.52 (0.97)	4.53 (0.99)	4.52 (0.96)	0.71
Change in LDL-C (mmol/L)	-1.96 (0.81)	-1.84 (0.70)	-1.86 (0.75)	-1.95 (0.80)	-1.96 (0.73)	0.92
Total cholesterol (mmol/L)	6.88 (1.10)	6.66 (1.04)	6.77 (1.07)	6.86 (1.09)	6.86 (1.05)	0.86
Triglycerides (mmol/L)	1.61 (0.45)	1.37 (0.38)	1.40 (0.40)	1.53 (0.75)	1.55 (0.75)	0.23
Antihypertensives (hypertension), n (%)	1426 (46.5)	4320 (48.4)	1530 (45.4)	1379 (46.4)	1410 (47.4)	0.44
Diabetes, n (%)	691 (22.5)	2433 (27.3)	834 (24.8)	678 (22.8)	680 (22.9)	0.98
Myocardial infarction, n (%)	107 (3.5)	254 (2.9)	81 (2.4)	93 (3.1)	93 (3.1)	1.00
Unstable angina pectoris, n (%)	45 (1.5)	129 (1.5)	46 (1.4)	44 (1.5)	43 (1.5)	1.00
Heart failure, n (%)	75 (2.4)	237 (2.7)	75 (2.2)	73 (2.5)	72 (2.4)	1.00
Arrhythmia, n (%)	182 (5.9)	480 (5.4)	175 (5.2)	177 (6.0)	180 (6.1)	0.64
Peripheral arterial disease, n (%)	54 (1.8)	130 (1.5)	56 (1.7)	52 (1.8)	44 (1.5)	0.47
Cerebrovascular disease, n (%)	242 (7.9)	665 (7.5)	208 (6.2)	181 (6.1)	172 (5.8)	0.66

Values are expressed as mean (SD) unless specified otherwise

HbA1c glycated haemoglobin, HDL high-density lipoprotein cholesterol, LDL low-density lipoprotein cholesterol

<sup>a</sup> T test for continuous variables and Chi-square test for categorical variable

Adapted from Hasvold P, Thuresson M, Sundström J, Hammar N, Kjeldsen SE, Johansson G, Holme I, Bodegård J. Association Between Paradoxical HDL Cholesterol Decrease and Risk of Major Adverse Cardiovascular Events in Patients Initiated on Statin Treatment in a Primary Care Setting. Clin Drug Investig. 2016 Mar;36(3):225-33 (16)

Patients were followed for up to 7 years, with a median follow-up of 2.0 years, including 14 198 patient-years. In the group with decreased HDL-C, the mean HDL-C reduction was 0.27 mmol/L. The risk of major cardiovascular events was 56% higher in the decreased HDL-C group ( $> 0.1$  mmol/L) compared with the unchanged HDL-C group ( $\pm 0.1$  mmol/L) (HR, 1.56; 95% confidence interval [CI], 1.12–2.16;  $p < 0.01$ ). The association between HDL-C change and the primary endpoint in the decreased and increased HDL-C groups showed consistent results in the sub-groups analyses: sex, primary/secondary prevention, with/without diabetes, and in patients above 75 years of age versus younger patients.

Eighteen per cent of patients initiated on statin treatment during the observation period were included in the study. The main reason for exclusion was lack of laboratory data, as only laboratory measurements from primary care were available. This favored the inclusion of patients with regular

primary care healthcare controls, for e.g. hypertension, diabetes, atrial fibrillation. A considerable proportion of secondary prevention patients with initiation of statin treatment in hospital did not have available pre-treatment HDL-C measurements and could therefore not be included. The exclusion of a significant proportion of patients might call into question the generalizability of the results. However, as the results were consistent in all subgroup analyses, with a numerically higher risk of reaching the composite endpoint with decreased HDL-C levels for all subgroups, thus the findings might be relevant to a broader patient population.

The study is observational and unmeasured confounders may have influenced the results. Patients with malignancy or history of alcoholism were not included in the study. Changes in body weight, smoking pattern, or physical activity might influence levels of HDL-C, the latter two of which are not systematically recorded in primary care records. Since smoking previously was reported to be associated with generally low HDL-C levels, it is likely that smokers would be in the unchanged group or increase group due to the regression to the mean effect in the study. Furthermore, if the increase in HDL-C was due to cessation of smoking, a decrease in HDL-C should be found more frequently in smokers. In Sweden, not only is the overall smoking practice low (<15%) but the likelihood of patients starting smoking during initiation of statin therapy can also be considered to be low. The inverse correlation between physical activity and HDL-C change is low and can therefore be considered to be of minor importance. A marked percentage increase in body mass index in patients with a reduction in HDL-C, when compared with patients with unchanged HDL-C levels was not observed.

Low compliance to statin treatment could potentially be a possible explanation for the findings. However, patients were only included in the analyses while on statin treatment, and only if the reported LDL-C reduction was greater than 0.5 mmol/L. The risk of the results being due to low compliance and/or statin response can therefore also be considered to be low.

The statin prescription pattern might be a source of confounding by indication. In the study, patients with high cardiovascular risk in general had a lower untreated LDL-C, and vice versa. This correlation between LDL levels and CVD risk has been reported previously in a real-life clinical setting. However, no correlation between LDL-C change and HDL-C change was found, as also supported by a previous report. A prescription bias based on low HDL-C levels might also be a source of explanation for the findings. As low HDL-C is not a reason for initiation of statin treatment in Sweden, it is not likely that HDL-C should be affected by confounding by indication. Furthermore, there was a mean difference of 1.1 mg of simvastatin between the decrease and unchanged groups after propensity score matching.

Analytical and biological variation of HDL-C values may be a potential source of misclassification into the different HDL-C change groups. In Sweden, HDL-C samples are generally analyzed at regional

central laboratories, which all participate in national quality and standardization programs since end of the 1980s. The analytical variation for HDL-C in the Swedish external quality assurance program is between 3% and 4% (at the level of 1.68 mmol/L), while the biological variation of HDL-C is approximately 7%. Patients in the study had to have a decrease in HDL-C of more than 0.1 mmol/L, and the average HDL-C decrease was 0.27 mmol/L. The conservative estimations of the HDL-C variation support the notion that the magnitude of the observed HDL-C decrease was sufficient.

Furthermore, similar associations with baseline cholesterol parts were observed (HDL-C, plasma triglycerides (TG), and LDL-C) on HDL-C change pattern in the study compared to what have been reported in randomized clinical trials. Thus, patients with high HDL-C had higher likelihood of HDL-C reduction and patients with low HDL-C and higher associated cardiovascular risk at baseline would more likely be identified for the HDL-C decrease group (16).

### 9.3.3 Paper III

In paper III, data were extracted from primary medical records at 71 primary care centers as described in paper II and linked data from NPR, the National Cause of Death register and Statistics Sweden (socio-economic status; educational level).

Patients of both sex with hypertension at the included primary care centers from 1999 to 2007, who were prescribed for the first time either enalapril or candesartan, with or without a fixed combination with hydrochlorothiazide, were eligible for inclusion. Exclusion criteria were a recorded diagnose or drugs prescribed for CVD, diabetes, chronic kidney disease or malignancy.

Time to event end-points were analyzed using Cox proportional hazards regression models. Time to diabetes or CVD was analyzed separately.

Of 43,576 eligible patients; 33,946 (77.9%) were prescribed enalapril and 9,636 (22.1%) candesartan. In the 27,592 excluded patients, 66% (n=22,221) were in the enalapril group and 56% (n=5,371) in the candesartan group. The remaining study population consisted of 15,990 patients; 11,725 treated with enalapril and 4,265 with candesartan. All 71 primary care centers prescribed both enalapril and candesartan, although in various ratios. The patient characteristics in the two groups before and after propensity score matching are presented in the table below.



### 9.3.4 Baseline data for 15,990 hypertensive patients without previous cardiovascular disease and diabetes

Variable	Unmatched			Propensity score matched		
	Enalapril (n = 11 725)	Candesartan (n = 4265)	P-value	Enalapril (n = 1111)	Candesartan (n = 1111)	P-value
Age (years)	61.0 (12.1)	60.0 (11.6)	<0.01	59.6 (10.8)	59.7 (10.7)	0.81
Women, n (%)	6216 (53)	2431 (57)	<0.01	582 (52)	583 (53)	1.00
Body mass index (kg m <sup>-2</sup> )	29.2 (5.3)	28.9 (5.2)	0.10	28.8 (4.8)	29.5 (5.2)	0.04
Systolic blood pressure (mm Hg)	163.3 (19.1)	162.0 (19.2)	<0.01	161.5 (18.7)	161.7 (18.3)	0.80
Diastolic blood pressure (mm Hg)	91.8 (10.6)	91.8 (10.4)	0.94	92.2 (10.2)	92.1 (10.2)	0.71
Total cholesterol (mmol l <sup>-1</sup> )	5.9 (1.0)	5.8 (1.0)	0.11	5.9 (1.0)	5.9 (1.0)	0.88
LDL cholesterol (mmol l <sup>-1</sup> )	3.6 (0.8)	3.6 (0.8)	0.90	3.6 (0.8)	3.6 (0.8)	0.79
HDL cholesterol (mmol l <sup>-1</sup> )	1.4 (0.3)	1.4 (0.3)	0.92	1.4 (0.3)	1.3 (0.3)	<0.01
Triglycerides (mmol l <sup>-1</sup> )	1.6 (0.8)	1.6 (0.8)	0.37	1.6 (0.7)	1.7 (0.8)	0.12
Glucose (mmol l <sup>-1</sup> )	5.4 (1.1)	5.3 (1.1)	<0.01	5.3 (1.3)	5.3 (1.3)	0.63
HbA1c (%)	4.9 (0.7)	4.7 (0.5)	<0.01	4.7 (0.5)	4.9 (0.7)	<0.01
Serum creatinine (μmol l <sup>-1</sup> )	79.6 (16.7)	82.3 (16.2)	<0.01	81.4 (16.1)	82.0 (16.2)	0.41
Potassium (mmol l <sup>-1</sup> )	4.1 (0.3)	4.1 (0.3)	0.12	4.1 (0.3)	4.1 (0.3)	0.57
Thiazides, n (%)	2082 (18)	525 (12)	<0.01	204 (18)	197 (18)	0.74
Calcium channel blockers <sup>a</sup> , n (%)	1181 (10)	555 (13)	<0.01	172 (15)	181 (16)	0.64
Beta blockers, n (%)	2855 (24)	1050 (25)	0.74	351 (32)	366 (33)	0.52
Statins, n (%)	749 (6)	290 (7)	0.37	137 (12)	137 (12)	0.95
Socio-economic status <sup>b</sup> (low/medium/high)	35/33/32	31/32/37	<0.01	33/29/39	32/30/38	0.76
Percentage of patients hospitalized for any reason <sup>c</sup>	10.6%	11.1%				
Number of visits in primary care <sup>c</sup>	2.0	2.0				
Total number of diagnoses set (100 patients year <sup>-1</sup> ) <sup>c</sup>	196.3	196.7				

Abbreviations: HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein. The numbers in brackets represents s.d., where no other description is given. <sup>a</sup>Dihydropyridine substances. <sup>b</sup>Educational level. <sup>c</sup>Within 15 months before the start of study.

Adapted from Hasvold LP, Bodegard J, Thuresson M, Stalhammar J, Hammar N, Sundstrom J, et al. Diabetes and CVD risk during angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker treatment in hypertension: a study of 15,990 patients. *J Hum Hypertens*. 2014;28(11):663-9 (34)

During the study period, no difference in blood pressure between the two treatment groups was observed, and the proportion of patients with blood pressure recordings was similar in both treatment groups after one year of treatment. During the observation period, 38.7% (n= 4,538) patients were discontinued from the enalapril treated group and 27.1% (n= 1,157) from the candesartan group. During a mean follow-up of 1.84 years, 36,482 patient-years, the risk of new diabetes onset was lower in the candesartan group (hazard ratio (HR) 0.81, 95% confidence interval (CI) 0.69–0.96, P=0.01) compared with the enalapril group. No difference between the groups was observed in CVD risk (HR 0.99, 95% CI 0.87–1.13, P=0.86).

The additional sensitivity analyses results with adjustments for baseline HbA1c, blood glucose and BMI were consistent with the results from the main analysis for diabetes. The same result was also observed when diabetes diagnoses set within 6 and 12 months after the start of study were excluded. In propensity score-matched analyses, candesartan patients had a lower risk of diabetes development, HR 0.63 (95% CI 0.42-0.96, P=0.03).

The unadjusted risk of CVD was lower in candesartan patients than in enalapril patients (HR 0.87, 95% CI 0.76-0.98, P=0.02). When adjusting for covariates (age, sex, index year, socio-economic status), the risk was similar in the two groups. Similar results were observed when multiple

imputations were performed for systolic blood pressure. In the propensity score-matched analysis, the HR of CVD was 0.83 (95% CI 0.56 - 1.24, P=0.37)

In depth understanding for why physicians chose enalapril or candesartan for treatment for hypertension can only be explored by quality interviews with the prescribing physicians, data which was not available in this study. Data on smoking and physical activity was missing for the majority of patients, and was therefore not included in the analyses. The general socioeconomic status was lower in the enalapril group, and potentially more patients could be expected to smoke in this group or have a different physical activity profile. The difference in socioeconomic status is however, adjusted for in all the analyses. No difference was observed between the two groups in the proportions of patients with COPD diagnose and or use of COPD medications, which is closely related to smoking. Nor was there a difference in mean weight during follow up or any differences in how the patients were treated and followed up before and after start of study medication in recorded data.

A potential explanation of the finding of more new diagnoses of diabetes in the enalapril group could be “opportunistic diagnosis” due to a potential increased number of patient visits to primary care in this group who had a higher non-cardiovascular disease burden. However, the frequency of primary care visits, diagnoses, laboratory/blood samples data and hospitalizations prior to the start of the study did not differ markedly between the two groups, suggesting similar needs for medical consultations at baseline. No major difference in number of annual primary care visits or blood samples taken between the two treatment groups during follow-up was observed. The finding of increase number of diabetes diagnoses in the enalapril group did not follow the general trend regarding other diagnoses during the observation period as the number of other diagnoses made during the study was higher in the candesartan group. This does not support the possibility of a general higher disease burden in the enalapril group.

Enalapril and candesartan have the same prescribing indications in Sweden; both are indicated for hypertension and heart failure but not for renal diseases. However, The ACEis were available before the ARB class and thus gained hard endpoint documentation and CVD indications (heart failure, myocardial infarction) earlier. More patients (11.2%) were excluded for earlier diabetes and CVD in the enalapril group. Patient records in primary care were searched for chronic kidney disease, diabetes and CVD diagnoses and drugs up to 5-6 years before inclusion. The same diagnoses were also searched for in the NPR, which has a national coverage since 1987. The combination of these two search techniques, should therefore have lowered the risk of undetected diabetes and CVD prevalence at baseline.

When including patients over a long-time span, an important potential confounding factor could have been variations in hypertensive treatment over time, favoring inclusion either in the enalapril or candesartan group. Alterations in the Swedish reimbursement system for the use of RAAS inhibiting drugs for hypertension in 2008 are an example. Qualifications for reimbursement for hypertension from this date required that patients should start with an ACEi and ARBs should be prescribed as a second line treatment for patients with side effects on ACEi treatment or as add on therapy (heart failure). These requirements were implemented earlier in some areas of Sweden. The annual frequency of inclusion to the enalapril or candesartan group from 1999 to 2007 reflects these changes; by a relatively higher use of enalapril from 2005. In order to minimize the possible effects of temporal changes, index year (start of treatment) was included as covariate/adjustment in all analyses. The same results were observed when we excluded patients included in 2005-2007 from the study (34).

#### 9.4 PRIMARY CARE DATA FROM SWEDEN

As mention earlier, and illustrated by papers II and III, Sweden could potentially be an ideal country for retrieving data from primary care having electronic recording of patient medical data (EMRs) in almost all primary care centers since 2005, and to a large extent using server based journal systems. This potentiates data extraction by tailored extraction programs from a large number of medical records simple and feasible. The most frequently used method in Sweden is the Pygargus Customized eXtraction Program (CXP), which was used in paper II and III. This method has been used in more than 50 studies (33).

The technical aspects of the extraction method have been validated. The program extracted 100% of the relevant cases, with a specificity of 99.9% (33). Furthermore, in a manual comparison of data from 100 randomly selected patient journals at 25 primary care centers, no discrepancies were found when journal data and data in the study database was compared (17).

Since both primary and secondary care in Sweden utilize the same disease coding system (ICD-10), the disease management at different care giving levels can be followed. In addition, the quality of available clinical data in the EMRs, for example laboratory samples, are generally considered valid, as samples are commonly analyzed at regional central laboratories, all of which have participated in national quality and standardization programs (49).

##### 9.4.1 Limitations with primary care data from Sweden

There are limitations with Swedish EMR data. First, there is a potential variability in completeness of data across different patient populations as data are entered by GPs during routine consultations, and not in a structured uniform way optimal for research purposes. Thus, patients with more severe

conditions may potentially have more extensive follow up data, for example blood pressure and laboratory samples (17). If a patient move or change to another primary care center, then this patient will be lost to follow-up for primary care data, however, not for national register data.

Secondly, as EMR data must be collected from each individual primary care center, and the centers must individually accept extraction of data, hence there will be a selection of centers which accept participation in the studies/extraction programs. Potentially, there is a risk that participating centers might have a better or different standard of care than non-participating centers. However, when selecting centers there is normally an attempt to select representative samples of primary care centers regarding localization, rural vs non-rural and publicly funded vs private centers in order to have a representative sample of primary care centers of Sweden.

Third, the access to data is limited as there is no public registers for primary care data and no nationwide possibility of extracting data. Today, EMR data is only delivered by private vendors or for selected regions of Sweden as for example for the Stockholm region, where administrative data (diagnosis, visit dates, prescriptions) from primary care is available and linkable to national registers (50). However, these data do not include clinical data (blood pressure, weight, laboratory samples etc).

#### 9.4.2 Swedish primary care data compared to other data sources

There are countries other than Sweden which might have an easier access to primary care data. As already mentioned, UK with the well-established CPRD and THIN databases covering approximately 6-9% of the UK population are examples. However, data not for all of these primary care centers are linked with hospital data, currently covering approximately 60% of the UK practices (40), thus limit the access to hospitalized diagnosed based endpoints. In the Netherlands, the General Practitioner (GP) Database comprise data from electronic patient records registered by GPs for a catchment area representing 2.5 million residents, thus a smaller proportion of the total country population compared to the data used in papers II and III (51). However, in both UK and the Netherlands primary care centers must accept participation in the databases, thus implying a potential selection bias of participating centers as in Sweden. Furthermore, these databases extract data from routine primary care clinical practice, where data is not recorded for the purpose of research, and thus the potential challenge with different coverage of data/follow-up pattern in different patient populations is present also here. However, in the CPRD data base, various clinical awareness programs have increased the recording of different clinical data in a consistent way in the recent years (40).

Again, Taiwan is in a rather unique situation, where there is access to primary care data at a nationwide level, linkable to other data sources.

## 9.5 STATISTICAL METHODS

In recent years, real world data has increasingly been used to study differences in outcomes between various treatment groups. However, due to the nature of the data, the allocation to different treatment groups is not randomized, and thus there is always a risk that any observed difference in outcome between groups is caused by confounding factors still residing in the material.

In statistics, a confounder (also confounding variable or confounding factor) is a variable that influences both the dependent variable and independent variable causing a spurious association (52).

In register based studies on outcome of different drug therapies, a special type of confounding that may occur in is confounding by indication (53). This terminology is used when conditions determining the selections of drugs also are potentially linked to the outcome. The comparison of ACEi and ARB in paper III can be used to illustrate this phenomenon. ACEis have gained an earlier and often broader indication/endpoint data (heart failure, myocardial infarction, renal failure, diabetes) compared to the ARBs, which were introduced later to the market. Even for treatment of hypertension, there is a potential risk that ACEis therapy will be associated with a higher CV risk than ARBs. However, this finding may be a result of confounding by indication as patients treated with ACEi are more likely higher to have a higher CV risk (although potentially not (yet) recorded as a diagnosis), simply because this treatment is often prescribed for high risk conditions (heart failure, myocardial infarction).

Since the prescribing pattern of drugs is inflected by many factors (e.g. new indications, changed reimbursement criteria's), the characteristics of the patients treated can change during a drug's lifecycle. When this happens, i.e. when confounding by indication changes over time, calendar time might be a confounder or a proxy for other confounders (17, 54).

One way of potentially reducing the effect of confounding in observational research is to have access to a complete set of clinical variables that are possible affecting the risk. For example, in paper III where the aim was to study the effect of blood pressure lowering drugs on CV outcome and diabetes, it was essential to have access to blood pressure values, weight, laboratory test results (diabetes status) and socio economics status, all known to be associated with CV and diabetes risk.

The conventional method used to adjust for baseline differences between treatment groups in observational research is covariate adjustment, where relevant patient variables are included in a

regression model. A rule of thumb is to have at least 10 events per covariate included in the model, meaning that not all covariates (despite being identified as clinically important) can be included in the model (55, 56). Furthermore, the selection of which covariates to include in the regression model might not be straight forward, as there is a risk of over adjustment if too many variables describing the same underlying risk are included. An example of the difficulties posed may be related to the description of diabetes disease severity; e.g. which of HbA1c or blood glucose is the most appropriate and important laboratory variable to actually describe severity?

DAGs (directed acyclic graphs) are tools developed to describe the rationale behind the selection of the covariates in regression models (57). However, this method is still based on casual assumptions and the principal beyond this approach is little understood and it difficult to communicate outside the expert epidemiology community.

As an alternative or a compliment to multivariate adjusted methods, various matching methods have been developed which for several reasons are becoming gradually more popular in observational register studies. Among the most frequently used matching methods in observational register studies is the Propensity Score (PS) matching. A PS is defined as the probability of a patient being assigned to a treatment, given a set of covariates (58).

The estimated PS for a subject can be denoted by  $Pr(z|x)$ , where  $z$  is the treatment (0/1) and  $x$  is observed covariates. Since the PS is a probability, it ranges from 0 to 1. If two subjects have the same PS, then they will have the same chance of receiving a given treatment given available co-variates (59).

As the PS summarizes all patient characteristics into a single covariate, there is not limitation on number of covariates that can be included in the model. However, within large datasets, it recommended to include all variables that are potentially related to the outcome, whereas in smaller datasets, is recommended to only include variables that are strongly associated with outcome (56).

The PS can be used in the outcome model by different approaches: matching, stratification, inverse probability weighting, and use of PS as a covariate (55). As PS matching is a commonly used method, and used in paper II and III, I will focus on this method only.

The PS has the important balancing property that patients with the same propensity score administered either treatment A or B will typically have comparable distributions of measured covariates (60). This often facilitate the communication of the study results, as the baseline table will be presented in a format that mimics an RCT, with (negligible) differences between the treatment

groups, and thus many of the audience will accept the groups as comparable, and the discussion regarding potential unbalanced groups is often reduced.

PS matching also highlight areas of the covariate distribution where there is not sufficient overlap between the treatment groups, which is not done in multivariate adjusted methods. It will only include patients in the analysis where there is a sufficient covariate overlap, an important benefit in data sets with unbalanced patient covariates (60). However, caution should still be taken when interpreting the results of the outcome analysis, as they are only applicable for the patients where there is sufficient covariate overlap.

However, use of a propensity score matching does not resolve the problem with unmeasured/unknown confounding in observational register studies, and unlike in randomized trials, one cannot expect the balance in distributions of covariates included in the propensity score to be extended to (unmeasured) covariates not included in the propensity score (61).

Paper III (2014) and II (2016) were written in the period where there was a trend in comparative effectiveness papers from using covariate adjustment analysis to more use of propensity score matching methods.

In paper III (2014), patients with a history of chronic kidney disease, diabetes and CVD diagnoses were excluded since these were the study outcomes, and to reduced potential confounding by indication, thus excluding almost 50% of all available patients due to these criteria. As a main analysis, a multivariate adjusted method including clinically identified covariates known for affecting the outcome was used. The main analysis was supported by several sensitivity analyses, including more covariates (which was not present for all patients). Furthermore, imputation of missing values for example, systolic blood pressure, was also applied. One main sensitivity analysis included a propensity score matched analysis. The table below from the paper gives an interesting overview of how the different analysis methods affects the results.

### 9.5.1 Effect of additional adjustments and different analysis methods on clinical outcome

	Number of patients		HR, new-onset diabetes	HR, CVD
	Enalapril, n	Candesartan, n		
Unadjusted	11 725	4265	0.77 (95% CI 0.66–0.90)	0.87 (95% CI 0.76–0.98)
Primary adjusted results <sup>a</sup>	11 725	4265	0.81 (95% CI 0.69–0.96)	0.99 (95% CI 0.87–1.13)
+ systolic BP (Multiple imputed values) <sup>b</sup>	11 725	4265	0.80 (95% CI 0.68–0.94)	0.92 (95% CI 0.81–1.05)
+ systolic BP (available values) <sup>b</sup>	8881	2849	0.79 (95% CI 0.65–0.96)	0.97 (95% CI 0.83–1.13)
+ HbA1c <sup>b</sup>	1151	428	0.79 (95% CI 0.58–1.07)	–
+ blood glucose <sup>b</sup>	7338	2256	0.78 (95% CI 0.64–0.96)	–
+ BMI <sup>b</sup>	2896	772	0.86 (95% CI 0.97–1.15)	–
Excluding patients diagnosed within 6 months after the start of the study <sup>c</sup>	11 520	4212	0.87 (95% CI 0.72–1.05)	0.98 (95% CI 0.86–1.12)
Excluding patients diagnosed within 12 months after the start of the study <sup>c</sup>	11 443	4185	0.88 (95% CI 0.72–1.10)	0.97 (95% CI 0.85–1.11)
Propensity score analysis <sup>d</sup>	1111	1111	0.63 (95% CI 0.42–0.96)	0.88 (95% CI 0.56–1.24)

Abbreviations: BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; HR, hazard ratio. <sup>a</sup>Adjusted for age, gender, index year and socio-economic status. <sup>b</sup>Added adjustments to primary adjustments. <sup>c</sup>Primary adjustments. <sup>d</sup>Matched for gender, age, index year, systolic blood pressure, total cholesterol, blood glucose, socio-economic status, beta blockers, statins, calcium antagonists and thiazides.

Adapted from Hasvold LP, Bodegard J, Thuresson M, Stalhammar J, Hammar N, Sundstrom J, et al. Diabetes and CVD risk during angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker treatment in hypertension: a study of 15,990 patients. *J Hum Hypertens*. 2014;28(11):663-9 (34)

If the data were to be reanalyzed today, the likely statistical option would be a main propensity score matched model, based on the full study population excluding patients with diabetes prior study start. The PS model would only include patients where there was a sufficient covariate overlap between the ACE and ARB groups, thus likely handling the confounding by indication challenge in a more improved way than excluding all patients with chronic kidney disease and CVD diagnoses. Furthermore, it is also reason to believe that a larger proportion of patients by this could have been included in the analysis, as many of the excluded patients could have been matched, thus making the results more representative for a broader real life population.

A potential limitation with a propensity score method of the full patient population is however that variables (diagnoses and events) are normally entered into the propensity model as dichotomic variables, for example myocardial infarction (yes/no), heart failure (y/n), or PAD (y/n). Thus, the severity of these the different diagnosis or the time period after an event (for example myocardial infarction), i.e. a potential difference in risk, although same diagnosis, is not taken into account. Since the two treatment groups were highly unbalanced regarding (CVD) risk initially, it is potentially likely that there will still be a higher risk in the group with a higher initial risk, even after propensity score matching.

A major advantage with the used current analysis method, it that the effect of adding the different covariates easily can be observed. However, the point estimate of HR did not change much by adding more covariates into the model, and since the number of available patients is decreasing, some of the results are not statistically significant.



In paper II (2014), the selected main analysis was a propensity score matching based on the whole study population. Confounding by indication was not an issue in this study, as statins are not likely prescribed based on HDL-C values.

A major advantage of using propensity score matching in this study, besides the possibility to include many variables in the model, was the possibility to include both baseline LDL-C and LDL-C change on statin treatment as variables, thus thereby control for pre-statin LDL-C value and LDL-C change on statin treatment.

## 10 FUTURE PERSPECTIVE

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Register data is in many countries today recognized as a valuable source for research and knowledge, and efforts are made to provide access to more data sources and thereby to further broaden potential research questions. For example, currently data on laboratory samples and drug treatment given in a hospital setting are missing at a nationwide level in the Nordic countries. However, it is likely that laboratory data will be available in Denmark at nationwide level, since it is already available at regional level covering 33% of the population (62). Access to in-hospital drug data is becoming increasingly more important due to the nature of e.g. newer expensive oncology therapies that are given in an in-hospital setting. In many disease areas, especially within the area of cardiovascular disorders, this type of data is sometimes presently available in Swedish disease specific quality registers. However, this is not the case for many therapy areas, and work is undertaken in the Nordic countries to have access to these data at a nationwide level.

In Sweden there is ongoing work to have access to hospital drugs data at a national level i.e., to develop a national register of hospital-administered drugs (63). This work, initiated in 2011, has resulted in 4 published reports evaluating the technical and legal aspects of such a register (63-65). The progress is slow however, and if the aim is a register with hospital drugs in near future, the relevant authorities will have to intensify these efforts (59).

In Norway, there is an ongoing health authority driven project with the aim of having an implemented joint electronic patient journal system covering all data from primary care to hospital care and other types of care givers. As a part of the strategy behind this initiative, is easy research access, meaning all (drug) treatment from primary care to in-hospital can be analyzed. The aim is to have a pilot of this system up and running in parts of Norway already in 2018 (66).

Also in Denmark, it is likely that in-hospital drug treatment data will become available in the near future as in-hospital dispensing data from hospital pharmacies will be accessible for research. And it is likely that laboratory data will be available in Denmark at nationwide level, since it is already available at regional level covering 33% of the population (58).

Another major trend within register based research, is the application of new research methodology to overcome the shortcomings within register based research due to underlying confounding. Within the comparative effectiveness research field, the best assets of register studies including large, unselected populations, real world follow up, is combined with randomization to different treatment options of interest, thus avoiding the underlying problems with confounding. Sweden has been a pioneer country in this area conducting the first large study of this type with the TASTE (Thrombus

Aspiration in ST- Elevation Myocardial Infarction in Scandinavia) trial (67). The TASTE trial compared the effectiveness of intracoronary thrombus aspiration plus primary percutaneous coronary intervention (PCI) with PCI alone on 30-day mortality in patients with ST-segment elevation myocardial infarction using the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) with randomization to the different treatment arms (67). Several studies of this type are now ongoing in Sweden using randomization with follow up of patients in quality registers.

Similar study methodology, where randomization to different treatments is combined with usual clinical practice follow up using electronic medical journal data, is also utilized in studies in the primary care settings. UK seems to be one of the leading countries in this development of research methodology (68).

Sweden has been and is an attractive country for register research with its national registers and quality registers in combination with primary care data. However, this is a highly competitive area, and other countries might become more attractive for this type of research due to more complete laboratory data and data on drug treatment in a hospital setting. Also, the access to primary care data in Sweden could be more facilitated. However, Sweden is currently leading the development of studies combining randomization and follow up using data from register in hospital settings.

## 11 CONCLUSIONS

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Data from Swedish health care registries, being nationwide and providing an opportunity for linkage with other registers by using mandatory personal identification number, provides an excellent data source for disease insights from various aspects. Paper I showed that almost 50% of PAD patients below 75 years of age, who were diagnosed in a hospital setting had additional CV risk factors, and one in five patients died within a year after PAD diagnosis. The presence of additional risk factors other than age was the main driver for both CV-related and non-CV-related costs. PAD-related costs including hospitalizations and out-patient care visits were the main contributory CV-related costs in the first year after diagnosis of PAD. Although the PAD population has a well-recognized high-CV risk, the major proportion of hospitalization costs for PAD patients are not related to CV disease.

Very few registers outside Scandinavia can provide a similar comprehensive description of the outcome, use of healthcare resources, and costs over time for all patients with a hospital diagnosis of PAD in a longitudinal, nationwide setting.

Furthermore, the combination of nationwide Swedish health care register data and data extracted from primary care medical records is a research method which can be used to study risk predictors and outcomes of existing treatments for a large part of the population, providing rapid results at a low cost. In paper II it was shown that two-thirds of statin-naïve patients initiating statin treatment had a change in their HDL-C level, and the degree of change was similar to that observed in randomized clinical trials. A paradoxical decrease in HDL-C of (0.1 mmol/L) was associated with a 56% increase in major adverse cardiovascular events compared with unchanged HDL-C levels. No association between increased HDL-C levels and risk of major adverse cardiovascular events was observed.

While it in paper III was shown that in the management of primary hypertension (patients without diabetes or cardiovascular disease), candesartan treatment compared with enalapril treatment was associated with a risk reduction of new-onset diabetes, while no difference was observed between the two treatments in prevention of cardiovascular outcomes. Patients treated with enalapril had a shorter treatment period, indicating a lower tolerability for enalapril compared with candesartan.

However, access to data from primary care in Sweden is limited as there is no public registers for primary care data and no nationwide possibility of extracting data.

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# Long-term cardiovascular outcome, use of resources, and healthcare costs in patients with peripheral artery disease: results from a nationwide Swedish study

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## Aims:

Data on long-term healthcare costs of patients with peripheral artery disease (PAD) is limited, and the aim of this study was to investigate healthcare costs for PAD patients at a nationwide level.

## Methods and results:

A cohort study including all incident patients diagnosed with PAD in the Swedish National Patient Register between 2006–2014, and linked to cause of death- and prescribed drug registers. Mean per-patient annual healthcare costs (2015 Euros [€]) (hospitalisations and out-patient visits) were divided into cardiovascular (CV), lower limb and non-CV related cost. Results were stratified by high and low CV risk.

The study included 66,189 patients, with 221,953 observation-years. Mean total healthcare costs were €6,577, of which 26% was CV-related (€1,710), during the year prior to the PAD diagnosis. First year after PAD diagnosis, healthcare costs were €12,549, of which €3,824 (30%) was CV-related and €3,201 (26%) lower limb related. High-risk CV patients had a higher annual total healthcare and CV related costs compared to low risk CV patients during follow-up (€7,439 and €1,442 versus €4,063 and €838). Annual lower limb procedure costs were €728 in the PAD population, with lower limb revascularisations as key cost driver (€474).

## Conclusion:

Non-CV related hospitalizations and outpatient visits were the largest cost contributors for PAD patients. There is a substantial increase in healthcare costs in the first year after being diagnosed with PAD, driven by PAD follow-up and lower limb related procedures. Among the CV-related costs, hospitalisations and outpatient visits related to PAD represented the largest costs.

## Keywords

Nationwide register data • peripheral artery disease • healthcare resource use • healthcare costs

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## Introduction

Peripheral artery disease (PAD) has been recognized as a major contributor to the cardiovascular (CV) health burden.<sup>1,2</sup> Peripheral artery disease is a highly prevalent atherosclerotic syndrome affecting approximately 20% of people over 60 years of age in Sweden, and estimates [assessed using the ankle-brachial index (ABI)] have shown a recent increase in prevalence worldwide (of 23% during the last decade).<sup>3,4</sup>

Peripheral artery disease patients are at high risk of experiencing major CV events (MACE), which are associated with substantial impairment in quality of life and increased morbidity rates.<sup>5–8</sup> Thus, PAD is associated with a substantial economic burden both in terms of prevention and treatment of MACE and when managing lower limb-related symptoms and procedures.<sup>2</sup>

Previous studies have found that PAD patients are even more costly than patients with coronary artery disease (CAD) or cerebrovascular disease (CVD), having a 2-year cumulative cost of nearly USD 12 000, where half of the hospitalization costs are limb-related and half are due to treatment of MACE.<sup>2</sup> Despite the high prevalence of PAD, very few studies have investigated the long-term use of resources and costs after diagnosis. In addition, the relationship between costs related to PAD and total healthcare costs requires clarification.

As PAD is associated with high risk of MACE and mortality, with an increasing trend over time, the costs to healthcare in the long-term should also be acknowledged. In this observational study, we investigated CV outcome and long-term CV resource use and total healthcare costs for patients, before and after diagnosis of PAD in a Swedish nationwide setting.

## Methods

### Overview

In this observational cohort study, we retrieved data from three mandatory Swedish nationwide registries: the Swedish National Patient Register (NPR), the Swedish Prescribed Drug Register (SPDR), and the Swedish Cause of Death Register. The Swedish NPR covers more than 99% of all somatic and psychiatric hospital discharges, with inpatient admission and discharge dates, and also main and secondary diagnoses according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision [ICD-10].<sup>8</sup> The SPDR has data on all prescription medications dispensed by all pharmacies in Sweden.<sup>9</sup> Individual patient-level data from the registers were linked using the mandatory and unique Swedish personal identification numbers, which were subsequently replaced with study identification numbers before further data processing.

The study protocol was reviewed and approved by the regional ethics committee of the University of Gothenburg, Sweden (reference number: 649-14). Linkage of data was performed by the Swedish National Board of Health and Welfare. The linked database was managed by the Institute of Medicine at the Sahlgrenska Academy, Gothenburg, Sweden.

### Population

All patients with a first time primary or secondary diagnosis of PAD in a hospital setting (as inpatient or outpatient) [ICD-10 I70.0 (atherosclerosis of aorta), I70.2 (atherosclerosis of arteries of extremities), or I73.9 (claudicatio intermittens)] between 2006 and 2013 were included. The index date was defined as the date of the first recorded PAD diagnosis during

the specified observation period. Follow-up ended when a patient died or at the end of the observational period (January 2014). In Sweden, the diagnosis of PAD in a hospital setting is normally based on the medical history and on results of a clinical vascular examination including the ABI test.

Baseline characteristics and data on medication use were retrieved from the NPR and SPDR registers.

The population was stratified by age and risk profile at index date:

- Patients aged <65 years
- Patients aged 65–75 years
- Patients aged >75 years
- Patients with none of the following comorbidities in their previous medical history were defined as low-risk patients: diabetes mellitus, myocardial infarction (MI), stroke, heart failure, and chronic renal dysfunction.
- Patients with one or more of the following comorbidities were defined as high-risk patients: diabetes mellitus, MI, stroke, heart failure, or chronic renal dysfunction.

### Clinical outcomes

The primary endpoint of MACEs was a composite of hospitalization with a main diagnosis of non-fatal MI (ICD-10: I21), non-fatal IS (ICD-10: I63-I64), or CV death (ICD-10 codes I00–I99). Lower limb revascularization was defined as an open or endovascular procedure as captured in NPR based on procedure codes (see Supplementary Material online).

### Resource use

Data on hospitalizations and outpatient care visits were collected from the NPR. In cases where a subsequent hospitalization occurred without a calendar day between the discharge date and the new admission date, a single episode of hospitalization was recorded. When a patient had both a primary and a secondary diagnosis, the primary diagnosis defined the event type.

Resource use associated with CV disease included hospitalizations, outpatient care visits, and drug use. All non-procedural lower limb-related events were included in the category 'CV events'. Lower limb procedures included only invasive procedures for treatment of PAD. Non-CV-related care included all hospitalizations, outpatient care visits, and drug use that were not related to a diagnosis of CV as defined in ICD-10.

The Prescribed Drug Register included data on dispensed, prescribed drugs in terms of substance, formulation, dose, and date of administration. Cardiovascular drugs included drugs in the ATC class C: anti-platelets, warfarin, statins, NOACs, nitrates, and anti-hypertensives. Non-CV drugs were defined as all drugs not included in the ATC class C.

The major items of resource use and unit costs are listed in Supplementary material online, *Table S4a–d*.

### Unit costs

Each recorded hospitalization and outpatient care visit was assigned a 2015 diagnosis-related group (DRG) weight, which was multiplied by the most recent 2015 cost per weight.<sup>11</sup> In cases of missing DRG codes in the 2015 DRG catalogue, older DRG catalogues were used to apply the correct weight. If DRG codes recorded before 2015 had been stratified into several DRG codes in the 2015 DRG catalogue, a weighted average of these weights was applied. Irrespective of the year in which the DRG code was recorded, all costs were multiplied by the most recent cost per weight.

The daily cost of a drug was calculated by multiplying the average dose by the most recent retail price available.<sup>12</sup>

All costs were converted to euros using an average 2015 exchange rate, according to the European Central Bank: 1 euro (EUR) = 9.35 Swedish crowns (SEK).

## Analysis

Baseline characteristics are presented as mean and standard deviation for continuous variables and absolute and relative frequencies for categorical variables. Follow-up data were collected from the time of the index diagnosis of PAD until death or the end of follow-up. The frequency and proportion of patients with the primary composite endpoint were assessed and a Kaplan–Meier analysis was performed to estimate the cumulative probability of the primary composite endpoint during study follow-up. If one patient had several events, only the first was used in the survival model. Results are presented as hazard ratios (HRs) and 95% confidence intervals (CIs).

Resource use was calculated for each year, i.e. 1 year before initial PAD diagnosis, the year after being diagnosed with PAD (starting from the hospital admission date, or the date recorded for the outpatient visit when the PAD diagnosis was established), and the 5 years that followed. Patients contributed to a particular year of analysis if they died during the year or had a full year of exposure. Thus, a patient dying after 1.5 years of follow-up contributed to Year 2 whereas patients who were censored at 1.5 years due to no more follow-up time did not.

Mean healthcare costs per patient per year were estimated by applying unit costs to the corresponding resource use items. If a patient had both a PAD CV-related diagnosis and a lower limb procedure performed at the same visit, the costs were reported as being lower limb-related.

Costs were differentiated into CV-related, non-CV-related, and lower limb-related and presented as subgroups stratified by a combination of risk profile and age.

Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) and R version 3.2.3.

## Results

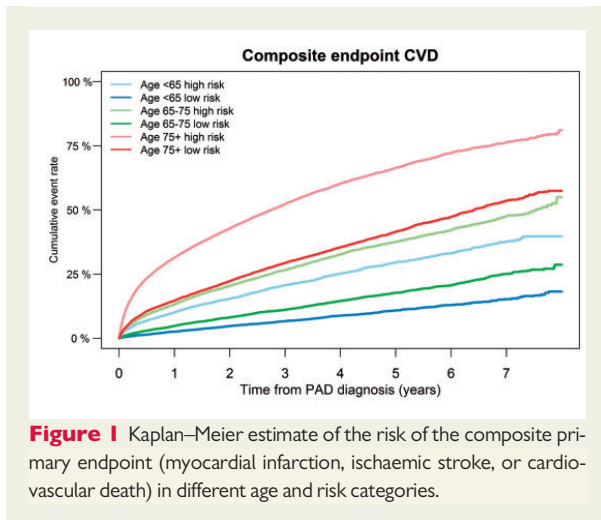
Overall, 141 266 patients with a diagnosis of PAD were identified, 66 189 of whom had their first PAD diagnosis established during the observation period and were included in the study. Peripheral artery disease was mainly diagnosed at hospital outpatient visits (71%), and was the main reason for hospital contact in 77% of the patients. Mean length of follow-up was 2.8 years, with a maximum of 8 years, resulting in a total of 184 614 patient-years of follow-up.

The youngest and oldest patient groups with a high risk of CV had different profiles. Compared with subjects over 75 years of age, a higher proportion of subjects less than 65 years old were men (69% vs. 50%), had diabetes (71% vs. 53%), and had renal insufficiency (11% vs. 4%), whereas cancer (9% vs. 23%) and stroke (16% vs. 29%) were more prevalent in older patients. Statin use was more common in the youngest patients than in the oldest (75% vs. 39%), who in turn used more analgesics (49% vs. 70%, Table 1). A higher proportion of older women (over 75 years old) were categorized as being low-risk (61% than women aged 75 years or younger (47%).

**Table 1** Description of analysis population after being diagnosed with peripheral artery disease

	Age <65 high-risk n = 5050	Age <65 low-risk n = 5752	Age 65–75 high-risk n = 10 733	Age 65–75 low-risk n = 9908	Age 75+ high-risk n = 21 068	Age 75+ low-risk n = 13 678	Total n = 66 189
Age (SD)	59.5 (3.8)	59.3 (3.9)	70.4 (3.1)	70.1 (3.1)	84.0 (5.2)	83.4 (5.3)	75.6 (10.3)
Gender (Female)	1567 (31.0)	2510 (43.6)	3719 (34.7)	4914 (49.6)	10 595 (50.3)	8297 (60.7)	31 602 (47.7)
Aorta aneurysm	163 (3.2)	258 (4.5)	712 (6.6)	708 (7.1)	951 (4.5)	629 (4.6)	3421 (5.2)
Diabetes	3594 (71.2)	0 (0.0)	6977 (65.0)	0 (0.0)	9840 (46.7)	0 (0.0)	20 411 (30.8)
Hypertension	4284 (84.8)	2708 (47.1)	9585 (89.3)	6326 (63.8)	18 086 (85.8)	9397 (68.7)	50 386 (76.1)
Myocardial infarction	1409 (27.9)	0 (0.0)	3189 (29.7)	0 (0.0)	6391 (30.3)	0 (0.0)	10 989 (16.6)
Angina pectoris	1553 (30.8)	474 (8.2)	3700 (34.5)	1129 (11.4)	6754 (32.1)	1913 (14.0)	15 523 (23.5)
Ischaemic stroke	794 (15.7)	0 (0.0)	2433 (22.7)	0 (0.0)	6040 (28.7)	0 (0.0)	9267 (14.0)
Heart failure	1141 (22.6)	0 (0.0)	3303 (30.8)	0 (0.0)	10 464 (49.7)	0 (0.0)	14 908 (22.5)
Atrial fibrillation	636 (12.6)	205 (3.6)	2495 (23.2)	808 (8.2)	8823 (41.9)	2256 (16.5)	15 223 (23.0)
Major organ specific bleedings	433 (8.6)	231 (4.0)	1088 (10.1)	553 (5.6)	2941 (14.0)	1161 (8.5)	6407 (9.7)
Chronic renal insufficiency	548 (10.9)	0 (0.0)	862 (8.0)	0 (0.0)	951 (4.5)	0 (0.0)	2361 (3.6)
Chronic obstructive pulmonary disease	428 (8.5)	325 (5.7)	1448 (13.5)	961 (9.7)	2310 (11.0)	1027 (7.5)	6499 (9.8)
Cancer	449 (8.9)	563 (9.8)	1822 (17.0)	1750 (17.7)	4883 (23.2)	3013 (22.0)	12 480 (18.9)
Anti-platelets	3711 (73.5)	3689 (64.1)	7974 (74.3)	6767 (68.3)	14 893 (70.7)	8677 (63.4)	45 711 (69.1)
Clopidogrel	731 (14.5)	333 (5.8)	1463 (13.6)	638 (6.4)	2166 (10.3)	769 (5.6)	6100 (9.2)
Low dose aspirin	3525 (69.8)	3564 (62.0)	7455 (69.5)	6453 (65.1)	13 856 (65.8)	8233 (60.2)	43 086 (65.1)
Warfarin	479 (9.5)	243 (4.2)	1694 (15.8)	608 (6.1)	3843 (18.2)	1169 (8.5)	8036 (12.1)
Statins	3793 (75.1)	3383 (58.8)	7816 (72.8)	6168 (62.3)	8985 (42.6)	5301 (38.8)	35 446 (53.6)
Anti-hypertensives	4429 (87.7)	3095 (53.8)	9938 (92.6)	7007 (70.7)	19 842 (94.2)	10 908 (79.7)	55 219 (83.4)
Anti-diabetics	3263 (64.6)	17 (0.3)	6159 (57.4)	19 (0.2)	7915 (37.6)	20 (0.1)	17 393 (26.3)
Analgesics	2478 (49.1)	2124 (36.9)	5742 (53.5)	3957 (39.9)	14 851 (70.5)	8017 (58.6)	37 169 (56.2)

All data are n (%) unless stated otherwise. SD, standard deviation.



**Figure 1** Kaplan-Meier estimate of the risk of the composite primary endpoint (myocardial infarction, ischaemic stroke, or cardiovascular death) in different age and risk categories.

The overall 1-year cumulative incidence rates of the primary composite CV endpoint (MI, stroke, or CV death) and all-cause death were 16.6% and 21.1%, respectively.

In patients who were 75 years old or younger, the 1-year cumulative incidence rate for the primary composite endpoint was 12.2% in high-CV-risk patients and 4.0% in low-CV-risk patients. Corresponding figures for patients over 75 years of age were 31.4% in high-CV-risk patients and 14.7% in low-CV-risk patients (Figure 1).

## Procedures performed

In total, 23 481 lower limb revascularization procedures were performed during the study period. The cumulative incidence rate of lower limb revascularization procedures for the full study population was 23.2 (95% CI 22.9–23.5) at 1 year after being diagnosed with PAD. The cumulative probability of lower limb revascularization was 20.1 (95% CI 19.8–20.4) at 6 months and 27.6 (27.2–27.9) at 3 years (see Supplementary material online, Table S2). A larger proportion of high-risk patients underwent amputations, whereas the proportion of patients who underwent lower limb revascularizations was more similar across the low- and high-CV-risk populations and age categories (see Supplementary material online, Table S5).

## Pattern of resource use

One year before diagnosis of PAD, the mean total number of contacts per patient (i.e. hospitalization and outpatient care visits) was 4.05, with outpatient visits being the main reason for contact (mean number: 3.21) (Table 2). In the year following diagnosis of PAD, the mean total number of contacts increased to 6.36, with outpatient visits being the main reason for contact (mean number: 4.99). During the year after diagnosis of PAD, the mean number of CV-related hospitalizations and outpatient visits was 2.30, with PAD being the main reason for contact. The mean number of lower limb procedure contacts was 0.38 in the year after diagnosis of PAD, which became reduced to 0.04 in the subsequent years.

For the CV-related long-term drug therapy [such as low-dose aspirin, angiotensin-converting enzyme (ACE) inhibitors, and statins],

the average number of days on drug continued to be higher from the second year after the year of being diagnosed with PAD compared with the year before the PAD diagnosis.

## Healthcare costs

The mean annual total cost of healthcare in the year before the diagnosis of PAD was €6577, of which €1710 (26%) were CV event-related hospitalization costs and outpatient visits and €3748 (57%) were non-CV-related hospitalization costs and outpatient visits. Drug therapy was responsible for 17% of the total.

During the year after PAD diagnosis, there was a 90% increase in the mean total costs for all patient age and risk groups, totalling €12 549. Thirty per cent of this was attributed to CV-related hospitalizations and outpatient visits (€3824), with PAD-related follow-up being the main reason for hospital attendance (Table 2). Also, the number of lower limb-related invasive procedures increased during this year, with a total mean cost of €3201. Non-CV-related costs were not substantially different from those in the year before the diagnosis of PAD.

The mean total healthcare cost decreased from the second year after diagnosis of PAD and onwards, with lower mean total annual costs (€5750) than the year before PAD diagnosis. However, lower limb-related procedure costs remained higher throughout the study period, with a mean total annual cost of €728. The mean annual CV-related cost was €1140 after the first year of being diagnosed with PAD.

High-risk CV patients had higher total healthcare costs than low-risk CV patients after diagnosis of PAD, the mean annual costs being €7439 and €4063, respectively. Also, the mean CV-related hospitalization cost was higher in the high-CV-risk group than in the low-risk CV group: €1442 as opposed to €838.

After patients were diagnosed with PAD, CV drug treatment contributed least to healthcare costs in all the years studied (mean annual cost: €200). Both CV drugs and non-CV drugs showed a similar trend, with a higher observed cost in high-risk patients.

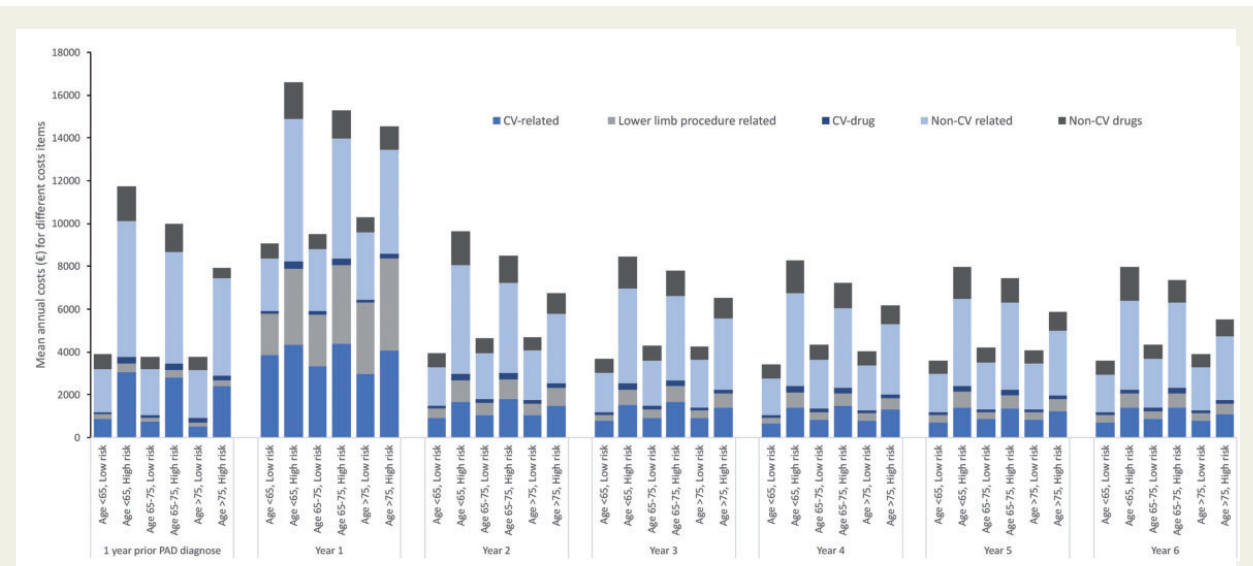
High-risk patients had higher costs associated with lower limb-related procedures (mean total: £3952) than low-risk patients (mean total: €2605) and for amputation in particular (€1703 vs. €629) (Figure 3). The selected CV-related costs were high in all risk groups and age categories, with a mean for all groups of €2071. In all patients, PAD-related costs (not including limb-related procedures) were the greatest costs within the selected CV category (52%), with coronary events and stroke (32%), and heart failure (13%) being observed as the other major CV cost drivers. Also, in the years that followed, total PAD-related costs remained the most important cost contributor among the different CV-related costs, although there was a shift in PAD costs to a larger proportion of limb procedure-related costs over time (Figure 4).

After being diagnosed with PAD, lower limb procedure-related costs were an annual major cost driver in the study population over time (mean: €728), with lower limb revascularizations being the main cost contributor (mean: €474) (Figure 4). The difference in lower limb procedure costs in high-risk and low-risk patients was mainly caused by the fact that there were more amputations in the high-risk CV population (Figure 3 and see Supplementary material online, Table S5).

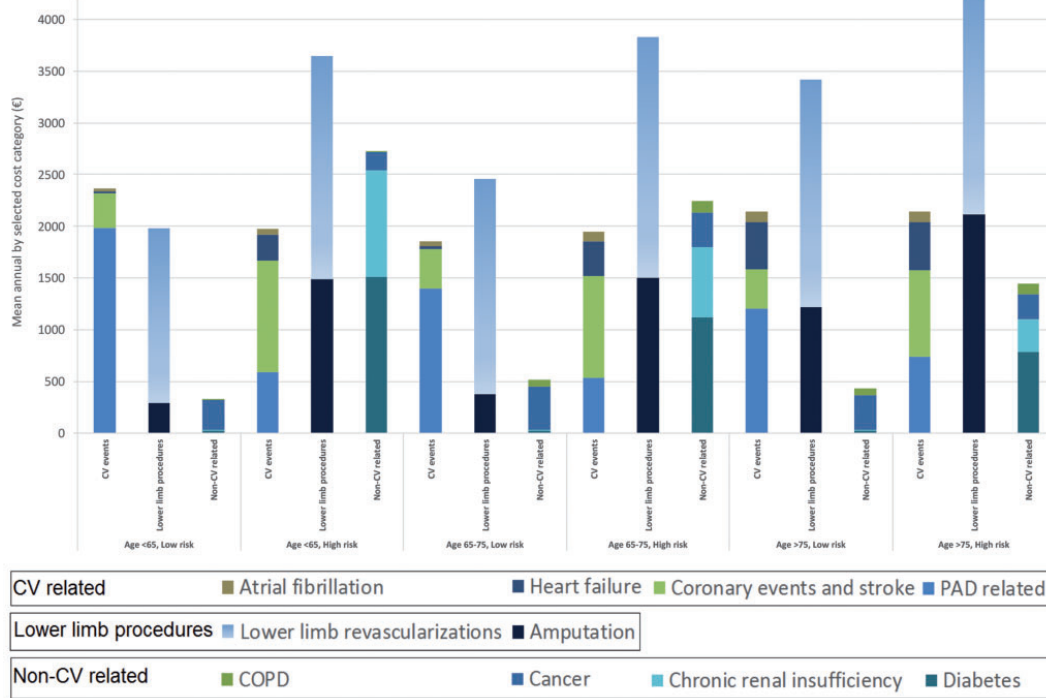
**Table 2** Resource use pattern over time, year 1 being first year after peripheral artery disease diagnosis

	1 year prior to PAD diagnosis	Year after diagnosis					
		1	2	3	4	5	6
Number of patients	66,189	53,024	42,032	32,547	24,338	17,610	11,938
<b>Hospitalizations</b>							
CV related care	0,27	0,47	0,18	0,17	0,15	0,15	0,14
Lower limb procedures	0,03	0,35	0,07	0,05	0,04	0,04	0,04
Non-CV related care	0,54	0,55	0,4	0,38	0,37	0,35	0,35
<b>Outpatient care visits</b>							
CV related care	0,32	1,83	0,53	0,4	0,36	0,35	0,35
Lower limb procedures	0	0,03	0,01	0	0	0	0
Non-CV related care	2,89	3,13	2,58	2,41	2,37	2,34	2,28
<b>Pharmaceuticals</b>							
Anti-platelets	169	245	238	238	239	237	235
Clopidogrel	14	30	24	24	24	25	26
Low dose ASA	155	226	220	219	220	218	215
Anticoagulants	20	23	24	24	24	24	26
Statins	105	183	179	182	184	186	184
Anti-hypertensives	270	281	281	282	282	283	284
Anti-diabetics	77	79	79	79	79	79	77
Analgesics	79	101	87	83	81	80	80

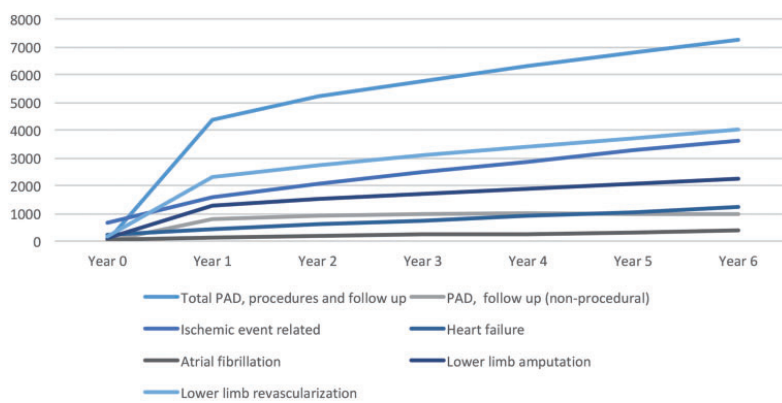
CV related care, lower limb procedures and non-CV related care resource utilization are reported in mean numbers of contacts for hospitalisations and outpatient care visits. Drug usage are reported in mean number of days (DDD).



**Figure 2** Annual costs per patient prior to and after peripheral artery disease (PAD), by cost category, age, and risk. cardiovascular (CV)-related: includes all ICD-10 CV 'I' diagnoses except PAD-related costs in combination with lower limb procedures. If a PAD patient had a hospitalization with a PAD diagnosis 'I' and a lower limb procedure, then the cost for this visit is reported as being lower limb procedure-related. Non-CV-related: all costs except costs related to CV (ICD-10 'I').



**Figure 3** Mean costs per patient during the first year after diagnosis of peripheral artery disease, by selected cost category, age, and risk. Coronary events: myocardial infarction and unstable angina pectoris. PAD-related, peripheral arterial disease (follow-up, not including lower limb procedures); COPD, chronic obstructive pulmonary disease.



**Figure 4** Cumulative cost during follow-up of selected diagnoses and procedures. Ischaemic event-related: myocardial infarction, unstable angina pectoris, and stroke. Peripheral arterial disease follow-up (non-procedural): follow-up of peripheral arterial disease, not including lower limb procedure.

## Discussion

One-third of the PAD population was over 75 years of age and was categorized as high-risk, but even among patients aged less than

75 years, more than 50% could be classified as high-risk, with diabetes and a history of coronary events being the most prevalent comorbidities. Within a year after diagnosis of PAD, more than one in five patients died and one in six experienced a MACE. Compared with



patients surviving an MI, PAD patients had a significantly higher 1-year mortality risk (21.1% vs. 13.2%) and showed a comparable CV risk (16.6% vs. 18.3%).<sup>13,14</sup>

In high-risk patients, the 1-year risk of CV events was increased three-fold for those less than 75 years old and doubled for those over 75 years, as compared with PAD patients without risk factors. The resource use and pattern of costs was associated with age and underlying risk, with the latter being the most important determinant of costs, as has also been observed in MI patients.<sup>15</sup> This study reports only hospitalization costs (including hospital-based outpatient visits), but other drivers of the total healthcare costs for these patients, as for example nursing home and primary healthcare costs were not included. Furthermore, wider data on community-care and patients' own costs and productivity impacts are not included.

Costs of hospitalizations and outpatient visits related to PAD were the greatest of the CV-related costs, particularly during the year after PAD was diagnosed. However, non-CV-related hospitalizations were the largest cost contributor overall, being approximately twice as frequent in Year 2 after PAD diagnosis, with five times as many outpatient care visits, as compared with CV-related visits. Interestingly, although the PAD population has a well-recognized high risk of CV, the major part of the hospitalization costs for PAD patients (including outpatient visits) is not related to CV diseases—with, for example, costs associated with diabetes and chronic renal insufficiency being larger cost contributors (Figure 3). It may not be relevant to focus only on CV-related risk prevention separately, but it is perhaps better to have a broader view when assessing risk and potential interventions for this patient population.

Despite generally having a higher CV baseline risk and more CV events than younger patients, patients over 75 years of age generally had lower CV-related costs. This might be explained by the fact that a lower proportion of elderly patients undergo expensive invasive heart related procedures as percutaneous coronary intervention or coronary artery bypass grafting in Sweden.<sup>16</sup> Also, the lower limb procedure-related costs, especially for amputations, and non-CV-related costs were substantially higher in the youngest age group (< 65 years), which may have been attributable to the high prevalence of diabetes (71%).

The total annual CV-related costs—excluding lower limb procedure costs—for PAD patients during long-term follow-up were higher than they are for MI patients, with mean of €1945 per patient as opposed to approximately €1700–1800 per patient,<sup>15</sup> an effect of the progressive, chronic nature of PAD.

Not surprisingly, the contributors to CV-associated costs are somewhat different in the MI and PAD populations. Myocardial infarction patients have more recurrent MIs, while PAD patients have more recurrent PAD manifestations with relatively fewer MIs. This is supported by the observation that the PAD-related costs due to hospitalizations and outpatient visits were the main contributors to CV-related costs for all patient categories, contributing to more than 50% of the CV-related costs in first year after diagnosis of PAD. In total, approximately 23 500 revascularizations were performed, and the majority within the first 6 months, which would explain the decline in PAD-related costs over time.

Lower limb-related procedure costs were a significant overall cost contributor at Year 1, both for low- and high-CV-risk patients

(Figures 2–4), but they decreased over time to be comparable with other studies where PAD procedure-related costs constitute only a modest fraction.<sup>1</sup> However, costs associated with amputations are higher in the high-CV-risk groups than in low-CV-risk patients, whereas the costs of lower limb revascularization are more similar in the different patient groups. This might be related to the inherently worse limb prognosis in patients with PAD in combination with diabetes, cardiac failure, or kidney failure, even when successful lower limb revascularization procedures are undertaken, due to having more severe lesions.

It is difficult to compare healthcare costs due to differences in study design and healthcare systems, but our data on total costs for the combination of CV-related and lower limb-related procedures are comparable to what has been reported previously for PAD patients in France and Germany,<sup>17</sup> but they are lower than data from the USA.<sup>2</sup>

Cardiovascular-related drug costs contributed least among the cost categories investigated. This is partly explained by the fact that most drugs given in association with CV disease today are generic, and have a low acquisition cost. Another contributing factor may be the still uncommon use of cardioprotective medications in PAD.

The present study had some limitations. Firstly, we did not have access to data describing the extent and severity of PAD, which may have an impact on the cost of treatment. Furthermore, the resource use and costs were divided into CV-related and non-CV-related, with a rather narrow definition of CV-related hospitalizations and outpatient care visits. A hospitalization was assigned an ICD-10 circulatory system diagnosis as the primary diagnosis to be categorized as CV, excluding CV-related hospitalization costs when attributable as for example a secondary diagnosis. As a registry data-based analysis, the study relied on ICD-10 codes for morbidity data, so the possibility of coding errors cannot be completely ruled out.

These data, however, provide a comprehensive description of the outcome, use of healthcare resources, and costs over time for all patients with a hospital diagnosis of PAD in a longitudinal, nationwide setting. These results provide information that will be useful for future healthcare planning and allocation of resources.

## Conclusions

Data from this nationwide study showed that almost 50% of PAD patients aged below 75 years who were diagnosed in a hospital setting had additional CV risk factors. One in five patients died within a year after PAD diagnosis. The presence of additional risk factors other than age was the main driver for both CV-related and non-CV-related costs. Peripheral artery disease-related costs including hospitalizations and outpatient care visits were the main contributory CV-related costs in the first year after diagnosis of PAD. Also, lower limb procedure-related costs were initially high, and remained so during subsequent follow-up of these patients. Although the PAD population has a well-recognized high-CV risk, the major proportion of hospitalization costs for PAD patients are not related to CV disease. Healthcare systems will need to consider preventive strategies and optimize costs of prevention in the growing PAD population.

## Supplementary material

Supplementary material is available at *European Heart Journal – Quality of Care and Clinical Outcomes* online.

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**Conflict of interest:** P.H., T.K., and S.J. are employed by AstraZeneca. M.T. is employed at Statisticon, of which AstraZeneca is a client. J.N, B.K, M.F and B.S report no conflict of interest.

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# Association Between Paradoxical HDL Cholesterol Decrease and Risk of Major Adverse Cardiovascular Events in Patients Initiated on Statin Treatment in a Primary Care Setting

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## Abstract

**Background and Objectives** Statin-induced changes in high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) are unrelated. Many patients initiated on statins experience a paradoxical decrease in HDL-C. The aim of this study was to evaluate the association between a decrease in HDL-C and risk of major adverse cardiovascular events (MACE).

**Methods** Data from 15,357 primary care patients initiated on statins during 2004–2009 were linked with data from mandatory national hospital, drug-dispensing, and cause-of-death registers, and were grouped according to HDL-C

change: decreased  $\geq 0.1$  mmol/L, unchanged  $\pm 0.1$  or  $\geq 0.1$  mmol/L increased. To evaluate the association between decrease in HDL-C and risk of MACE, a sample of propensity score-matched patients from the decreased and unchanged groups was created, using the latter group as reference. MACE was defined as myocardial infarction, unstable angina pectoris, ischaemic stroke, or cardiovascular mortality. Cox proportional hazards models were used to estimate relative risks.

**Results** HDL-C decreased in 20 %, was unchanged in 58 %, and increased in 22 % of patients initiated on statin treatment (96 % treated with simvastatin). The propensity score-matched sample comprised 5950 patients with mean baseline HDL-C and LDL-C of 1.69 and 4.53 mmol/L, respectively. HDL-C decrease was associated with 56 % higher MACE risk (hazard ratio 1.56; 95 % confidence interval 1.12–2.16;  $p < 0.01$ ) compared with the unchanged HDL-C group.

**Conclusions** Paradoxical statin-induced reduction in HDL-C was relatively common and was associated with increased risk of MACE.

**Electronic supplementary material** The online version of this article (doi:10.1007/s40261-015-0372-9) contains supplementary material, which is available to authorized users.

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## Key Points

Of patients newly initiated on statin treatment, one-fifth experienced a decrease in HDL-C.

This HDL-C decrease was associated with higher risk of major adverse cardiovascular events compared with unchanged HDL-C.

Statin induced HDL-C decrease might be more hazardous than previously recognised and patients should be monitored closely regarding potential cardiovascular risk.

## 1 Introduction

The role of high-density lipoprotein cholesterol (HDL-C) as a potential risk factor in the development of cardiovascular disease (CVD) is not fully understood. Epidemiological studies have reported an association between HDL-C single point measurements and risk of coronary heart disease (which forms a large proportion of CVD) [1–3]. Some guidelines recommend an HDL-C target above 1.0 mmol/L for men and above 1.2 mmol/L for women, [4] but such goals have also been questioned [5, 6]. Recent studies with novel HDL-C-raising therapies have not shown a clear preventive effect of increasing HDL-C on risk of CVD. Treatment with one such agent, torcetrapib, resulted in an increased risk of mortality and morbidity of unknown mechanism, whereas potential favourable effects of another agent, dalcetrapib, with respect to HDL-C were possibly offset by other unfavourable effects [7, 8].

Statins show various degrees of low-density lipoprotein cholesterol (LDL-C)-lowering and HDL-C-raising effects, [9] where the action on HDL-C is independent of the reduction in LDL-C [10]. It has been indicated from a meta-analysis that among statin-treated patients, HDL-C levels are strongly and inversely associated with the risk of major cardiovascular events [11]. Notably, a large proportion of patients experienced a paradoxical decrease in HDL-C following statin treatment initiation [10]. A recent study reported an inverse association between the paradoxical HDL-C decrease after initiation of statin therapy and major adverse cardiovascular events in patients with acute myocardial infarction [12]. It is possible that a reduction in HDL-C is associated with suboptimal protection against cardiovascular events [13].

The aim of this observational study was to investigate the association between paradoxical HDL-C decrease after initiation of statin therapy and major adverse cardiovascular events in a general primary care patient population.

## 2 Methods

The study protocol was reviewed and approved by the regional research ethics committee in Uppsala, Sweden (Reference number 2012/007) and registered at ClinicalTrials.gov (clinical trial identifier NCT01551784).

This study linked data from electronic patient records to hospital, drug-dispensing, and cause-of-death registers. Information on blood lipids and patient characteristics was extracted from primary care medical records [e.g. date of birth, gender, body weight, blood pressure, number of primary healthcare centre contacts, and diagnosis according to International Classification of Diseases, 10th

revision, Clinical Modification (ICD-10-CM) codes) using an established software system [14].

Data regarding morbidity and mortality were collected from the Swedish National Patient Register, inpatient (admission and discharge dates, and main and secondary diagnoses) and outpatient hospital care (number of contacts and diagnosis according to ICD-10-CM codes) registers, and the Swedish National Cause-of-Death Register (date and cause of death) [15]. Drug-dispensing data were collected from the Swedish Prescribed Drug Register.

Data linkage was performed by the Swedish National Board of Health and Welfare. The linked study database is owned and managed by the Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden. Personal identification numbers used to identify included patients in all healthcare contacts and were anonymised prior to further data processing.

The study population consisted of statin-naïve patients initiating a first statin treatment at 76 primary care centres in Sweden. To facilitate a representative selection of primary care centres in Sweden, a mix of rural and urban areas, public and private care providers, and small, mid-sized, and large primary care centres (all using the same electronic patient journal system) was included, corresponding to approximately 7 % of the Swedish primary care centres. Men and women were eligible for inclusion if they were aged 18–85 years and were prescribed statins [Anatomical Therapeutic Chemical (ATC): C10A A] between 1 January 2004 and 31 December 2009. Patients had to have HDL-C and LDL-C measurements recorded within 12 months prior to the start of statin treatment as well as a measurement after 10 days and within 12 months on treatment; patients with cardiovascular events before the first HDL-measurement on statin treatment were excluded. Patients with an LDL-C lowering of no more than 0.5 mmol/L were also excluded due to insufficient statin effect or indication of low compliance to statin treatment. Further exclusion criteria were prior history of alcoholism and on-going malignancy.

The date of first known statin dispense was defined as start of statin treatment. The start of the observation period for collecting endpoints was date of first HDL-C measurement on statin treatment. The end of the study observation was 31 December 2011, the end of statin treatment, or death. If a gap of more than 90 days was observed, based on available dispensed drug data, the end of statin treatment was defined as calculated days on last available dispensed drug package plus an additional 25 % of days based on the last dispensed drug pack size.

Two HDL-C groups were defined based on change in between last HDL-C measurement prior statin treatment and first HDL-C measurement on at least 14 days of statin treatment: HDL-C decrease: more than 0.1 mmol/L and

HDL-C unchanged group:  $\pm 0.1$  mmol/L. In addition, a group with more than 0.1 mmol/L increase in HDL-C was defined to explore the effect of HDL-C increase.

The analysis was performed in two patient samples; the matched sample, which included HDL-C decrease and unchanged HDL-C patients who fulfilled the inclusion and exclusion criteria and who could be propensity score matched for baseline characteristics regarding propensity of HDL-C decrease. The unmatched population used for sub-group analyses comprised all patients who fulfilled the inclusion and exclusion criteria.

The major adverse cardiovascular event (MACE) endpoint was a composite of hospitalisation for a primary diagnosis for myocardial infarction (ICD-10, I21), unstable angina pectoris (ICD-10, I20.0), ischaemic stroke (ICD-10, I63), or cardiovascular death (all primary causes of death diagnosed with ICD-10 codes I00–I99).

Differences in baseline data between the two HDL-C groups were tested by one-way ANOVA and Pearson's chi-square test according to the type of data. Differences between groups were considered statistically significant when  $p$  was less than 0.05.

Propensity score matching provides an alternative means to balance study groups in order to reduce confounding when randomisation is not possible [16–20]. Logistic regression models were included to estimate the propensity scores between the decreased and unchanged HDL-C groups, with the HDL-C decrease as the response variable and the following covariates: age, gender, baseline HDL-C, baseline LDL-C, LDL-C change on statin treatment, antihypertensive therapy, diagnosis of diabetes, heart failure, hypertension, angina pectoris, peripheral artery disease (PAD), and stroke.

The propensity scores were matched pairwise, with exact matching for prior myocardial infarction and use of calipers of width equal to 0.1 of the standard deviation of the propensity score. The matching procedure was performed using the Match function in the R package Matching [21]. The primary endpoint was analysed by a Cox proportional hazards model, using a grouped jack-knife estimation of the variance to take the correlation within pairs into account.

The association between HDL-C change and the primary endpoint in the decreased and increased HDL-C groups was studied in the following sub groups: gender (men/women), primary/secondary prevention, with/without diabetes, and in patients above 75 years of age versus younger patients. In the sub-group analyses, Cox regression with adjustment for age, gender, baseline HDL-C, baseline LDL-C, LDL-C change on statin treatment, antihypertensive therapy, diagnoses of diabetes, heart failure, hypertension, angina pectoris, PAD, and stroke was used.

An additional analysis was performed comparing the separate outcome of cardiovascular death or all-cause death, as well as a sensitivity analysis including patients with a LDL-C reduction of  $<0.5$  mmol/L.

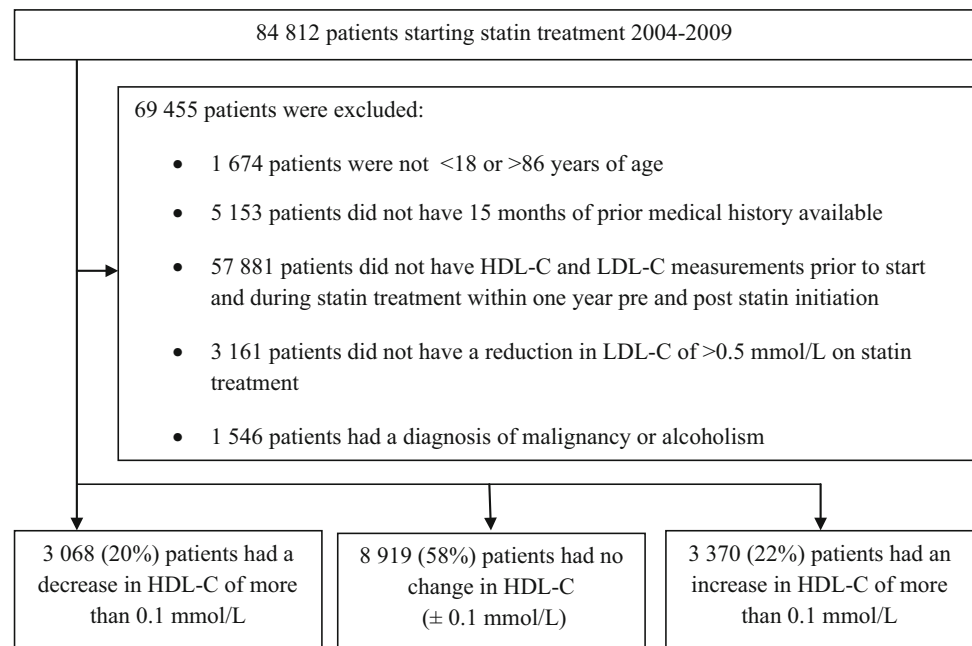
### 3 Results

In all, 84,812 patients were initiated on statin treatment during the observation period, of whom 15,357 (18 %) were eligible (Fig. 1). The main reason for exclusion was lack of recorded lipid measurements before and during statin treatment. Compared with the study population, the excluded patients were more often men, were older, and fewer had diabetes/more had CVD before statin treatment initiation (Table S1).

In the full eligible study cohort, baseline mean age was 62.7 years (range 19–85 years) and mean HDL-C was 1.48 mmol/L. The majority of patients (96 %) were initiated on simvastatin, with a mean dose of 20 mg/day (median 20 mg/day). Of these patients, 20 % had a decrease in HDL-C during the observation period, 58 % were unchanged, and 22 % showed an increase (Fig. 1). The patient group with a decrease in HDL-C comprised more women, had a higher HDL-C at baseline (1.69 mmol/L), less diabetes, compared with the unchanged HDL-C group (Table 1). The groups were similar regarding presence of cardiovascular diagnoses; myocardial infarction, angina pectoris, PAD, stroke or heart failure. The changes in HDL-C and LDL-C did not show any correlation (Fig. S1) [10].

The decreased and unchanged HDL-C groups showed a large degree of propensity score overlap (71 %), indicating that these groups were similar prior to the start of statin treatment. After matching, the decreased and unchanged HDL-C groups had similar baseline characteristics and LDL-C changes, with the exception of a higher simvastatin dose and lower triglyceride level in the decreased HDL-C group (Table 1). The mean baseline HDL-C was 1.69 mmol/L and mean LDL-C was 4.53 mmol/L, respectively. The median time from HDL-C measurement to the start of statin treatment was 12 days [interquartile range (IQR) 7–31 days], and the mean time from the start of statin treatment to the second HDL-C measurement was 84 days (IQR 48–148 days). Patients were followed for up to 7 years, with a median follow-up of 2 years, including 14,198 patient-years. In the group with decreased HDL-C, the mean HDL-C reduction was 0.27 mmol/L. The primary endpoint incidence rates (per 1000 patient-years) were 12.8 and 8.2 in the decreased and unchanged HDL-C groups, respectively.

**Fig. 1** Patient flow. HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol



The risk of major cardiovascular events was 56 % higher in the decreased HDL-C group compared with the unchanged HDL-C group [hazard ratio (HR), 1.56; 95 % confidence interval (CI), 1.12–2.16;  $p < 0.01$ ; Table 2; Fig. 2]. The difference between the two groups was due to ischaemic stroke (HR, 1.74; 95 % CI, 1.00–3.03;  $p = 0.05$ ), but was also driven by cardiovascular death (HR, 1.72; 95 % CI, 0.86–3.42;  $p = 0.12$ ).

### 3.1 Subgroup Analyses

The association between HDL-C change and the primary endpoint in the decreased and increased HDL-C groups showed consistent results in the sub-group analyses: gender, primary/secondary prevention, with/without diabetes, and in patients aged >75 years of age versus younger patients (Fig. 3; Table 3).

No difference in risk of major cardiovascular events was observed between the HDL-C increase group compared with the unchanged HDL-C group (HR, 1.05; 95 % CI, 0.82–1.34;  $p = 0.72$ ).

### 3.2 Sensitivity Analyses

The separate outcome of cardiovascular death (HR, 1.61; 95 % CI, 0.94–2.75;  $p = 0.09$ ) and all-cause death (HR, 1.30; 95 % CI, 0.92–1.85;  $p = 0.14$ ) showed similar results. To assess the impact of the 3161 patients with an LDL-C reduction of <0.5 mmol/L, they were included in the analyses which showed a similar risk (HR, 1.56; 95 % CI, 1.25–1.95;  $p < 0.01$ ).

## 4 Discussion

In this study, two-thirds of eligible patients initiating statin treatment had a change in their HDL-C level, and the degree of change was similar to that observed in randomised clinical trials [10]. A paradoxical decrease in HDL-C of >0.1 mmol/L was associated with a 56 % increase in major adverse cardiovascular events compared with unchanged HDL-C levels. The results were consistent across subgroups based on age, gender, presence of diabetes, primary and secondary prevention. No association between increased HDL-C levels and risk of major adverse cardiovascular events could be observed.

Results from a recent meta-analysis did not demonstrate an association between statin treatment, HDL-C change, and CVD risk [11]. Our patients had a relatively high untreated HDL-C level (1.48 mmol/L), in line with observations of untreated HDL-C levels in other Scandinavian studies, but in contrast with the recent publications [11, 21–23]. We observed a greater reduction in HDL-C (–0.27 mmol/L) compared with the meta-analysis (–0.13 mmol/L), and the relatively small HDL-C reduction in the meta-analysis might not have been sufficient to detect CVD risk associations. Furthermore, our findings are supported by a recent study which shows that a paradoxical decrease in plasma HDL-C levels after statin therapy is an important risk factor predicting long-term adverse cardiac events in patients with acute myocardial infarction [12].

Low single point measurements of HDL-C levels in patients receiving statin treatment have been reported to be associated with increased CVD risk, irrespective of the low



**Table 1** Baseline characteristics for patients with a decrease in HDL-C ( $\geq 0.1$  mmol/L), an increase in HDL-C ( $\geq 0.1$  mmol/L), or no change in HDL-C ( $\pm 0.1$  mmol/L) (unmatched and propensity score-matched populations)

Variable	Unmatched population			Propensity score-matched population		<i>p</i> value <sup>a</sup>
	Decreased ( <i>n</i> = 3068)	Unchanged ( <i>n</i> = 8919)	Increased ( <i>n</i> = 3370)	Decreased ( <i>n</i> = 2975)	Unchanged ( <i>n</i> = 2975)	
Women, <i>n</i> (%)	1872 (61.0)	4840 (54.3)	1997 (59.3)	1803 (60.6)	1798 (60.4)	0.92
Age (years)	62.3 (10.2)	62.6 (10.2)	63.0 (9.8)	62.2 (10.1)	62.3 (10.2)	0.64
Simvastatin, <i>n</i> (%)	2925 (95.3)	8510 (95.4)	3244 (96.3)	2835 (95.3)	2823 (94.9)	0.09
Dose (mg)	20.8 (9.7)	19.7 (8.7)	20.2 (8.8)	20.8 (9.7)	19.7 (8.4)	<0.01
Hospitalisations, number/year prior to statin start	0.2 (0.6)	0.2 (0.6)	0.19 (0.6)	0.2 (0.6)	0.2 (0.6)	0.16
Systolic blood pressure (mmHg)	144.6 (19.8)	143.6 (18.6)	144.0 (18.9)	144.6 (19.8)	143.3 (19.0)	0.02
Diastolic blood pressure (mmHg)	82.6 (10.4)	82.0 (10.1)	82.0 (10.4)	82.7 (10.4)	81.9 (10.2)	0.01
Body mass index (kg/cm <sup>2</sup> )	28.6 (5.0)	29.4 (5.0)	28.8 (4.9)	28.7 (5.0)	28.6 (5.2)	0.67
HbA1c (%)	5.5 (1.3)	5.7 (1.3)	5.64 (1.4)	5.6 (1.3)	5.6 (1.4)	0.77
HDL-C (mol/L)	1.69 (0.47)	1.41 (0.40)	1.44 (0.42)	1.66 (0.43)	1.66 (0.45)	0.95
LDL-C (mmol/L)	4.53 (1.00)	4.45 (0.95)	4.52 (0.97)	4.53 (0.99)	4.52 (0.96)	0.71
Change in LDL-C (mmol/L)	-1.96 (0.81)	-1.84 (0.70)	-1.86 (0.75)	-1.95 (0.80)	-1.96 (0.73)	0.92
Total cholesterol (mmol/L)	6.88 (1.10)	6.66 (1.04)	6.77 (1.07)	6.86 (1.09)	6.86 (1.05)	0.86
Triglycerides (mmol/L)	1.61 (0.45)	1.37 (0.38)	1.40 (0.40)	1.53 (0.75)	1.55 (0.75)	0.23
Antihypertensives (hypertension), <i>n</i> (%)	1426 (46.5)	4320 (48.4)	1530 (45.4)	1379 (46.4)	1410 (47.4)	0.44
Diabetes, <i>n</i> (%)	691 (22.5)	2433 (27.3)	834 (24.8)	678 (22.8)	680 (22.9)	0.98
Myocardial infarction, <i>n</i> (%)	107 (3.5)	254 (2.9)	81 (2.4)	93 (3.1)	93 (3.1)	1.00
Unstable angina pectoris, <i>n</i> (%)	45 (1.5)	129 (1.5)	46 (1.4)	44 (1.5)	43 (1.5)	1.00
Heart failure, <i>n</i> (%)	75 (2.4)	237 (2.7)	75 (2.2)	73 (2.5)	72 (2.4)	1.00
Arrhythmia, <i>n</i> (%)	182 (5.9)	480 (5.4)	175 (5.2)	177 (6.0)	180 (6.1)	0.64
Peripheral arterial disease, <i>n</i> (%)	54 (1.8)	130 (1.5)	56 (1.7)	52 (1.8)	44 (1.5)	0.47
Cerebrovascular disease, <i>n</i> (%)	242 (7.9)	665 (7.5)	208 (6.2)	181 (6.1)	172 (5.8)	0.66

Values are expressed as mean (SD) unless specified otherwise

*HbA1c* glycated haemoglobin, *HDL* high-density lipoprotein cholesterol, *LDL* low-density lipoprotein cholesterol

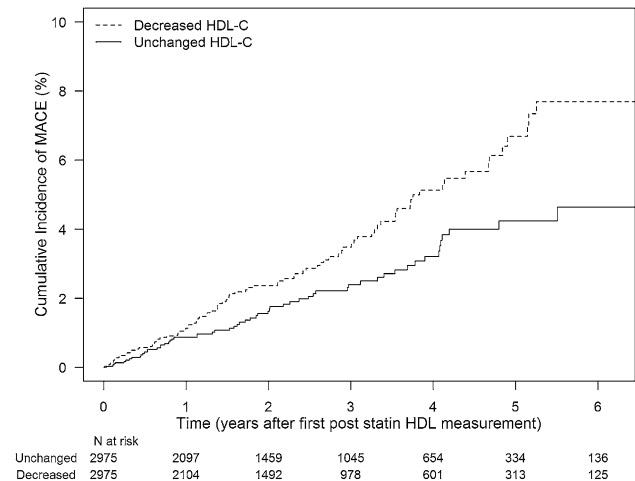
<sup>a</sup> *T* test for continuous variables and Chi-square test for categorical variable

**Table 2** Exposure time (years) in the propensity score-matched populations

	Unchanged HDL-C	Decreased HDL-C	Total
Maximum follow-up time	6.9	6.9	6.9
Median follow-up time	1.9	2.0	2.0
Total patient-years	7157	7041	14,198
Total number of events	59	90	149

LDL-C levels achieved [13]. We have shown that patients with a relatively high HDL-C (mean 1.48 mmol/L) newly initiated on cholesterol-modifying treatment (statin) and who experienced a consecutive HDL-C reduction have an increased cardiovascular risk, independently of baseline LDL-C and LDL-C change on statin treatment. Our findings are in line with previous observational data where a threshold for increased cardiovascular risk for HDL-C values below 1.3–4 mmol/L was observed [4]. Since the untreated HDL-C is relatively high in our material, this is the likely explanation for why we do not observe a reduced

cardiovascular risk with increased HDL-C values. A major decrease in HDL-C level, independent of the size of the LDL-C reduction, might cause a shift in cholesterol transport. Indeed, the one-third of patients initiated on statin therapy who had a paradoxical reduction in HDL-C level [10] may have a suboptimal balance of cholesterol in/out transport to/from the inner arterial wall. Other important cardiovascular risk-lowering properties of HDL-C include antioxidant, anti-apoptotic, anti-inflammatory, antithrombotic, and anti-proteolytic properties, which account for the direct protective action on endothelial cells

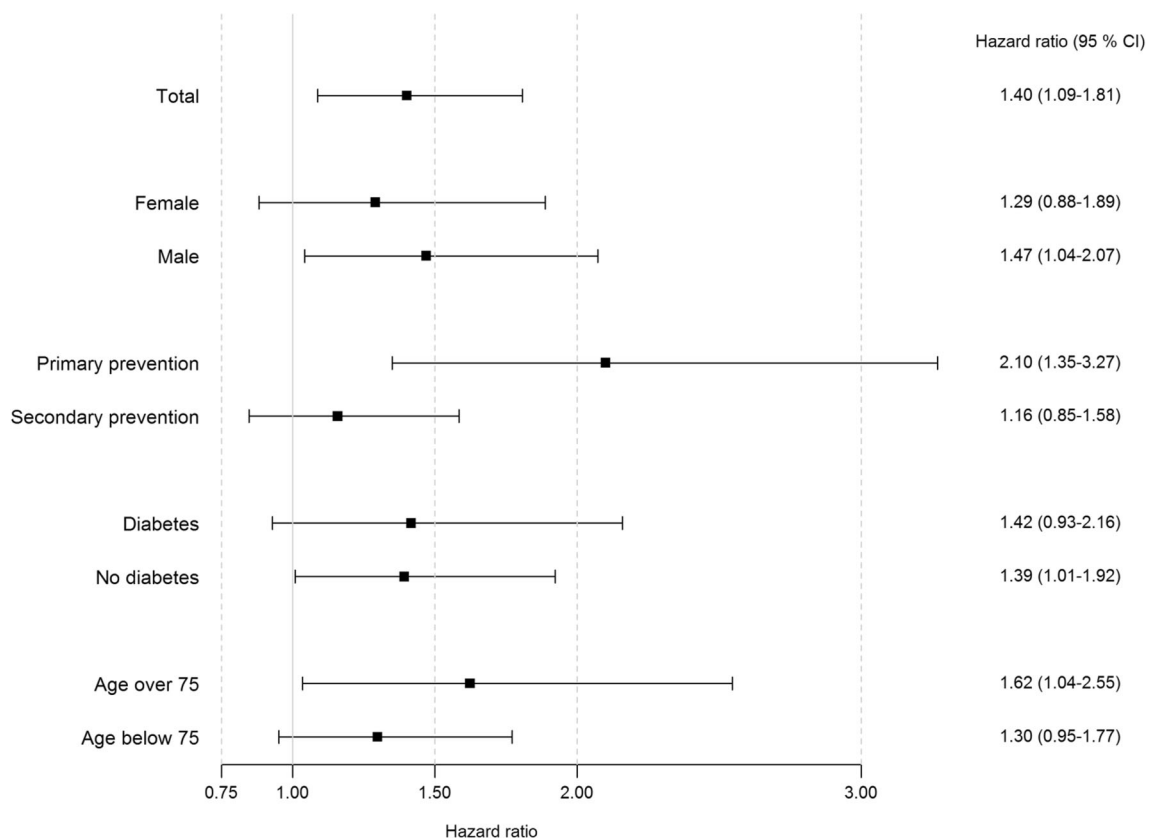


**Fig. 2** Kaplan-Meier plot of time to first major cardiovascular events for the decreased and unchanged HDL-C propensity score-matched populations. MACE major adverse cardiovascular events

[24]. The decrease in HDL-C might consequently negatively impact these protective actions. However, we believe that reduction of HDL-C per se is associated with increased cardiovascular risk and not necessarily a statin-specific effect. Thus, we would highlight the importance of non-

pharmacological efforts that will prevent HDL-C reductions, such as avoiding weight gain and/or maintaining physical activity levels.

The endpoint was a composite of hospitalisation with a primary diagnose of myocardial infarction, unstable angina pectoris, or ischaemic stroke, or cardiovascular death. An analysis of the separate endpoint components showed that risk of ischaemic stroke was statistically significant. The risks of coronary events and cardiovascular death were not significant, although the trends showed indication of similar directions/patterns. This finding might be somewhat surprising, as a predominant effect of statin treatment on coronary disease would be expected. However, as more patients in Sweden die outside hospital owing to coronary disease than owing to stroke, and a proportion of fatal coronary events occur in the out-of-hospital setting, stroke events were more likely to be a classified event in our study because more of these patients survived to hospitals [25, 26]. Similar results were observed when comparing outcome of separate analysis of cardiovascular death with all-cause death. Interestingly, the recent study which showed that a paradoxical decrease in plasma HDL-C levels after statin therapy initiation also had results driven by significantly higher incidence of stroke in the decreased HDL-C group [12].



**Fig. 3** Hazard ratio forest plot of major cardiovascular events in different sub-groups

**Table 3** Events and events rates for forest plot (Fig. 3)

	Unchanged HDL-C No of patients	Decreased HDL-C No of patients	Unchanged HDL-C No of events	Decreased HDL-C No of events	Unchanged HDL-C Events/1000 patient-years	Decreased HDL-C Events/1000 patient-years
Total	8919	3068	236	93	11.3	12.8
Female	4840	1872	98	43	8.5	9.7
Male	4079	1196	138	50	14.6	17.5
Primary prevention	5063	1838	62	34	5.3	8.1
Secondary prevention	3856	1230	174	59	18.8	19.0
Diabetes	2433	691	93	36	16.3	20.4
No diabetes	6486	2377	143	57	9.4	10.3
Age over 75 years	959	303	72	32	31.8	48.7
Age below 75 years	7960	2765	164	61	8.8	9.2

Eighteen percent of patients initiated on statin treatment during the observation period were included in the study. The main reason for exclusion was lack of laboratory data, as only laboratory measurements from primary care were available. This favoured the inclusion of patients with regular healthcare controls (hypertension, diabetes, atrial fibrillation) in primary care. A considerable proportion of secondary prevention patients with initiation of statin treatment in hospital did not have a pre-treatment HDL-C measurement available to us and were therefore not included (Table S1).

The exclusion of a significant proportion of patients might call into question the generalisability of the results. However, we found consistent results in all subgroup analyses, with a numerically higher risk of reaching the composite endpoint with decreased HDL-C levels for all subgroups (older vs. younger patients, men vs. women, primary vs. secondary prevention patients, and presence of diabetes). However, among secondary preventive patients, a smaller numerical difference in cardiovascular risk between unchanged and decreased HDL-C groups was observed. Secondary prevention, for patients recently experiencing a myocardial infarction or a stroke, might potentially have an initial increased thrombotic risk, which is more critical than the long-term effect caused by the atherosclerosis process. Altogether, this indicates that the study findings might be valid for a broad statin-treated population.

A further potential limitation regarding generalisability is the fact that the absolute majority of patients in Sweden are treated with relatively low doses of simvastatin. The frequent use of low-dose simvastatin might be the result of a stringent reimbursement regime, only allowing the use of high-potency statins in patients who do not reach treatment goals or in individuals who do not tolerate simvastatin. The effect on HDL-C change achieved by statins in general is reported to be independent of the reduction in LDL-C [10].

The present study is observational and unmeasured confounders may have influenced our results. Patients with malignancy or history of alcoholism were not included in the study. Changes in body weight, smoking pattern, or physical activity might influence levels of HDL-C, the latter two of which are not systematically recorded in primary care records. Since smoking previously was reported to be associated with generally low HDL-C levels, it is likely that smokers would be in the unchanged group or increase group due to the regression to the mean effect in our study [10, 27]. Furthermore, if the increase in HDL-C was due to cessation of smoking, a decrease in HDL-C should be found more frequently in smokers. In Sweden, not only is the overall smoking practice low (<15 %) but the likelihood of patients starting smoking during initiation of statin therapy can also be considered to be low. Furthermore, the effect of smoking cessation programmes in primary care is modest [28, 29]. The inverse correlation between physical activity and HDL-C change is low and can therefore be considered to be of minor importance [30]. We did not observe a marked percentage increase in body mass index in patients with a reduction in HDL-C, when compared with patients with unchanged HDL-C levels.

Low compliance to statin treatment could potentially be a possible explanation for our findings. However, patients were only included in the analyses while on statin treatment, and only if the reported LDL-C reduction was >0.5 mmol/L. The risk of the results being due to low compliance and/or statin response can therefore also be considered to be low.

The statin prescription pattern might be a source of confounding by indication. We found that patients with high cardiovascular risk in general had a lower untreated LDL-C, and vice versa. This correlation between LDL levels and CVD risk has been reported previously in a real-life clinical setting [31]. However, we found no correlation between LDL-C change and HDL-C change, as also

supported by a previous report [10]. A prescription bias based on low HDL-C levels might also be a source of explanation for our findings. As low HDL-C is not a reason for initiation of statin treatment in Sweden, though, it is not likely that HDL-C should be affected by confounding by indication. Furthermore, we observed a mean difference of 1.1 mg of simvastatin between the decrease and unchanged groups after propensity score matching. We do not think this minimal difference in dosing had any impact on the results.

Laboratory data were only available from primary care records. Biological and analytical variation of HDL-C values may be a potential source of misclassification into the different HDL-C change groups. However, we observed similar associations with baseline cholesterol parts [HDL-C, plasma triglycerides (TG), and LDL-C] on HDL-C change pattern in our study compared to those reported in randomized clinical trials [10]. Thus, in our study, patients with high HDL-C had higher likelihood of HDL-C reduction and patients with low HDL-C and higher associated cardiovascular risk at baseline would more likely be identified for the HDL-C decrease group. In Sweden, HDL-C samples are generally analysed at regional central laboratories, all of which have participated in national quality and standardisation programmes since the end of the 1980s [32]. The analytical variation for HDL-C in the Swedish external quality assurance programme is between 3 % and 4 % (at the level of 1.68 mmol/L) [31], while the biological variation of HDL-C is approximately 7 %. Patients in our study had to have a decrease in HDL-C of >0.1 mmol/L, and the average HDL-C decrease was 0.27 mmol/L. Our conservative estimations of the HDL-C variation support the notion that the magnitude of the observed HDL-C decrease was sufficient.

The present study also has several important strengths. First, the composite endpoint has been validated previously in Swedish studies [19]. Second, only statin-naïve patients were included in order to increase the likelihood of analysing the actual treatment effect on HDL-C levels. The observed HDL-C change pattern is similar to that observed in randomised clinical trials [10]. Third, our analyses carefully matched the patients for numerous cardiovascular diagnoses, risk factors, including baseline LDL-C, and LDL-C change on treatment, thus increasing the likelihood of similar baseline risk. Finally, using Swedish national health registers the follow-up was performed with basically no loss of events.

## 5 Conclusions

A marked proportion of patients newly initiated on statin treatment experienced a decrease in HDL-C. This decrease was associated with a higher risk of major adverse

cardiovascular events compared with patients in whom HDL-C levels were unchanged. Statin-induced increase in HDL-C was not associated with lower risk of major adverse cardiovascular events.

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**Contributors' statements** P Hasvold, M. Thuresson, G. Johansson, and J. Bodegård participated equally in the study conception, design, and statistical analysis planning. M. Thuresson was responsible for the statistical analyses, P. Hasvold for the manuscript draft and finalization, and G. Johansson for handling of data and the study database. All authors had access to study data, and had authority over manuscript preparation, approval of the final version, and the decision to submit for publication.

## Compliance with Ethical Standards

**Role of the funding source** Project management was provided by AstraZeneca. Data collection was performed by Pygargus AB, Stockholm, Sweden, and was funded by AstraZeneca. The statistical analysis was agreed on by the study steering committee, and data analysis was performed by the study database owner in collaboration with AstraZeneca. As members of the study steering committee, AstraZeneca took part in the interpretation of the data and the drafting of the manuscript. Editorial support was provided by Oxford PharmaGenesis Ltd, funded by AstraZeneca.

**Disclosures** Pål Hasvold is enrolled at the PhD School of the University of Oslo, Department of Medicine.

Pål Hasvold, Johan Bodegård, and Niklas Hammar are employed by AstraZeneca.

Marcus Thuresson is employed by an independent statistical consultant company, Statisticon AB, for which AstraZeneca is a client.

Gunnar Johansson has served on an advisory board arranged by AstraZeneca.

Johan Sundström serves on an advisory board for Itrim.

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## ORIGINAL ARTICLE

## Diabetes and CVD risk during angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker treatment in hypertension: a study of 15 990 patients

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Differences in clinical effectiveness between angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) in the primary treatment of hypertension are unknown. The aim of this retrospective cohort study was to assess the prevention of type 2 diabetes and cardiovascular disease (CVD) in patients treated with ARBs or ACEis. Patients initiated on enalapril or candesartan treatment in 71 Swedish primary care centers between 1999 and 2007 were included. Medical records data were extracted and linked with nationwide hospital discharge and cause of death registers. The 11 725 patients initiated on enalapril and 4265 on candesartan had similar baseline characteristics. During a mean follow-up of 1.84 years, 36 482 patient-years, the risk of new diabetes onset was lower in the candesartan group (hazard ratio (HR) 0.81, 95% confidence interval (CI) 0.69–0.96,  $P=0.01$ ) compared with the enalapril group. No difference between the groups was observed in CVD risk (HR 0.99, 95% CI 0.87–1.13,  $P=0.86$ ). More patients discontinued treatment in the enalapril group (38.1%) vs the candesartan group (27.2%). In a clinical setting, patients initiated on candesartan treatment had a lower risk of new-onset type 2 diabetes and lower rates of drug discontinuation compared with patients initiated on enalapril. No differences in CVD risk were observed.

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## INTRODUCTION

The renin-angiotensin system is targeted by two of the most widely used antihypertensive medication classes: angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs). ACEis and ARBs inhibit the renin-angiotensin system differently and may therefore differ in their preventive effects against both diabetes and cardiovascular disease (CVD).

ACEis and ARBs have been reported to be associated with a reduced onset of type 2 diabetes compared with placebo and other antihypertensive treatments.<sup>1–4</sup> A meta-analysis by Elliot and Meyer<sup>5</sup> demonstrated a lower risk of type 2 diabetes in patients treated with ARBs compared with ACEis. Possible explanations for this is the different effects of these medications on glucose metabolism through activation of different parts of the PPAR (peroxisome proliferator-activated receptors) system or more effective blockade of angiotensin type I receptors and the subsequent development of vascular insulin resistance and impaired endothelial nitric oxide-mediated relaxation.<sup>6,7</sup> However, no direct comparisons between ACEis and ARBs regarding risk of new-onset diabetes has previously been reported in patients with hypertension.

A few studies have compared the preventive effects of treatment with ACEis vs ARBs on CVD in high CV risk patients with neutral results.<sup>8,9</sup> Potential differences in the preventive effects of these drugs on CVD outcomes in uncomplicated hypertension patients are yet unknown.

Candesartan, being one of the two most frequently prescribed ARB in Sweden was chosen to represent the ARBs in this

comparison in order to reduce potential confounding. Candesartan was also shown to be more effective in reducing CVD than losartan, the other most commonly used ARB in Sweden.<sup>10</sup> Enalapril was chosen to represent the ACEis because of identical indications to candesartan and being the most frequently prescribed ACEi in Sweden (75% of patients receiving ACEis).

The aim of the study was to investigate differences in the risk for new-onset type 2 diabetes and CVD in patients initiated on antihypertensive treatment with enalapril or candesartan.

## PATIENTS AND METHODS

The study protocol was reviewed and approved by the Regional Research Ethics Committee in Uppsala, Sweden and registered with ClinicalTrials.gov, number NCT01152567.

Sweden has a tax-funded health-care system, providing primary and secondary care without out-of-pocket expenses and reimbursement for all prescribed drugs for chronic diseases, including hypertension. Patients are normally followed by a general practitioner.

## Study population

Men and women with hypertension identified at 71 primary care centers from 1 January 1999 to 31 December 2007, aged  $\geq 18$  years, who were prescribed for the first time either enalapril (Anatomical Therapeutic Chemical (ATC): C09A A02 or C09B A02) or candesartan (ATC: C09 CA06 or C09 DA06), with or without a fixed combination with hydrochlorothiazide, were eligible for the study. The first prescription of the study drug within the study period was defined as the start of the study. Exclusion criteria were a recorded diagnose of CVD, diabetes, chronic kidney disease or

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malignancy (data in Supplementary Table S1). Patients who were prescribed vitamin K antagonists, clopidogrel, acetylic salicylic acid, digitalis glycosides, aldosterone antagonists, loop diuretics, nitrates or anti-diabetes drugs within 15 months before the start of the study were considered to have potential CVD or diabetes and were excluded.

Data were extracted from the primary medical records at the primary care centers using an established software system.<sup>11</sup> Morbidity before and after the start date of the study was collected from the National Patient Register, inpatient (admission and discharge dates and main and secondary diagnoses) and outpatient hospital care.<sup>12</sup> Mortality during the follow-up was ascertained using the National Cause of Death register (date and cause(s) of death). Data regarding socio-economic status (educational level) were collected from the national censuses at Statistics Sweden. The linkage of data obtained from the national registers and primary care centers was performed by the Swedish National Board of Health and Welfare. Social security numbers, used to identify included patients in all health-care contacts, were replaced with study ID numbers before further data processing.

An attempt was made in the recruitment of study sites to ensure a representative selection of primary care centers in Sweden: a mix of rural and urban areas; public and private care providers; and small, mid-sized, and large primary care centers (data in Supplementary Table S2). The study sample represents approximately 7% of the total number of the primary care centers in Sweden.

#### Baseline examinations

Data on age, gender, blood pressure values and body mass index, laboratory/blood samples, diagnoses according to International Classification of Diseases, 9 and 10th revision, Clinical Modification (ICD-9/10-CM) codes, number of visits and prescribed drugs were extracted from the primary care journals. The baseline for the blood pressure value was calculated as the mean of the last three measurements during the time period 15 months before until 14 days after the start of enalapril or candesartan treatment. Blood pressure at 6 months was calculated as the mean of measurements 2 weeks to 6 months after the start of the study. From 12 months and onwards, 6-monthly blood pressures were calculated as the mean of measurements from 6 months before to 6 months after the specific time point.

#### Follow-up and outcomes

Patients were eligible for analysis while they remained on study drug treatment. The observation period ended on the date when the patient died, discontinued the study drug treatment, started a new C09-medication/renin-angiotensin system inhibiting drug or on 31 December 2007.

The criteria for the diagnosis of diabetes in Sweden is normally based on elevated plasma glucose values ( $>7.0 \text{ mmol l}^{-1}$ ) and/or a positive oral glucose tolerance test. The end point for diabetes was a recorded primary care or hospital discharge diagnosis of type 2 diabetes (ICD-9 code 250, ICD-10 codes E10-E14) and/or prescription of a drug within the ATC system class A10. This end point for diabetes diagnosis have been validated in other studies.<sup>13</sup> The end point for assessing CVD consisted of a recorded diagnosis of all non-fatal and fatal CVD (myocardial infarction, unstable angina, chronic ischemic heart disease, peripheral artery disease, heart failure, cardiac arrhythmias and stroke) as defined by ICD codes (see Supplementary Table S1).<sup>10</sup>

#### Statistical methods

The study database was owned and managed by the Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden. The data were processed and analyzed by an independent statistical contract company (Statisticon AB, Stockholm, Sweden).

All descriptive data are given as mean (s.d.) or percentage (%). Time to event end points were analyzed using the Cox proportional hazards regression models, and the results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs) and corresponding *P*-values. If one patient had several end points, only the first was used in the survival model. Time to diabetes or CVD was analyzed separately.

#### Selection of covariates for the primary analysis

The main analysis is an adjusted model with adjustment for age and gender at baseline, socio-economic status and year of the start of the

study. Patients with a history of renal disease, CVD and/or diabetes were excluded from this study. Age, gender, elevated blood glucose, overweight and low socio-economic status are known risk factors for diabetes.<sup>14–16</sup> High cholesterol and hypertension are additionally known risk factors for CVD.<sup>17</sup>

All included patients had hypertension, and there was no difference between the two treatment groups regarding baseline lipid values and statin use. The socio-economic status is associated with smoking pattern, overweight and physical activity, thus a risk factor for diabetes and CVD.<sup>16,18</sup> The treatment patterns (diagnoses, treatment targets) may change over time, and year of the start of the study was included as covariate.

The main analysis was supported by sensitivity analyses where additional covariates with incomplete coverage at baseline were included and analyses with exclusion of end points recorded within a specific time frame after the start of the study. Furthermore, for a complementary analysis, propensity scores were estimated corresponding to the probability of receiving the treatment given the baseline covariates. A matched propensity score analysis was performed in order to address confounding associated with the indication for treatment.<sup>19</sup>

#### Sensitivity analyses diabetes

For diabetes, additional sensitivity analyses were performed where baseline hemoglobin A1c (HbA1c), blood glucose and body mass index were included as additional covariates. The number and percentage of patients with high HbA1c ( $>7.0\%$ ) or blood glucose ( $>7.0$  and  $>10.0 \text{ mmol l}^{-1}$ ) values at baseline was also estimated. Analyses were performed where patients with high baseline HbA1c and blood glucose values were excluded. The diagnosis of diabetes within 6 and 12 months after the start of the study were also excluded in extra analyses for diabetes and CVD.

#### Sensitivity analyses for diabetes and CVD

Propensity score methods have become widely used tools for confounding control in non-randomized studies of drug effectiveness.<sup>19,20</sup> The propensity scores for receiving either enalapril or candesartan were calculated using a logistic regression model in which the dependent variable was use of enalapril or candesartan. Independent covariates included in the model were gender, age, year of the start of the study, systolic blood pressure, total cholesterol, blood glucose, socio-economic status, beta blockers, statins, calcium antagonists and thiazides as covariates. Blood glucose was selected as a covariate for laboratory samples related to diabetes, as the elevated blood glucose is the main diagnostic criterion for diabetes in Sweden. The resulting propensity scores were matched pair wise using callipers of width equal to 0.2 of the s.d. of the propensity score using the matching package in R.<sup>21,22</sup> Risk of new-onset diabetes and CVD were calculated using a Cox proportional hazards model stratified by the matched pairs.

For both end points, the same model for adjusted Cox regression with multiple imputation of systolic blood pressure as additional covariate was applied. The potential effect of variation in proportion of included patients per year in the two cohorts was also studied by analyzing the cohorts of patients included before and after 2005 separately. The presented *P*-values are not adjusted for multiplicity, and thus in the interpretation of the results one should take the total number of comparisons into account.

## RESULTS

Of the 43 576 eligible patients; 33 946 (77.9%) were prescribed enalapril and 9636 (22.1%) candesartan. In the 27 592 patients with exclusion criteria, 66% ( $n=22\,221$ ) were excluded in the enalapril group and 56% ( $n=5371$ ) in the candesartan group (Figure 1). The remaining study population consisted of 15 990 patients; 11 725 treated with enalapril and 4265 with candesartan. All 71 primary care centers prescribed both enalapril and candesartan, although in various ratios.

#### Baseline characteristics

The baseline characteristics for the included patients are summarized in Table 1. Compared with the candesartan patients, enalapril patients were slightly older (+ 1.0 years), less frequently

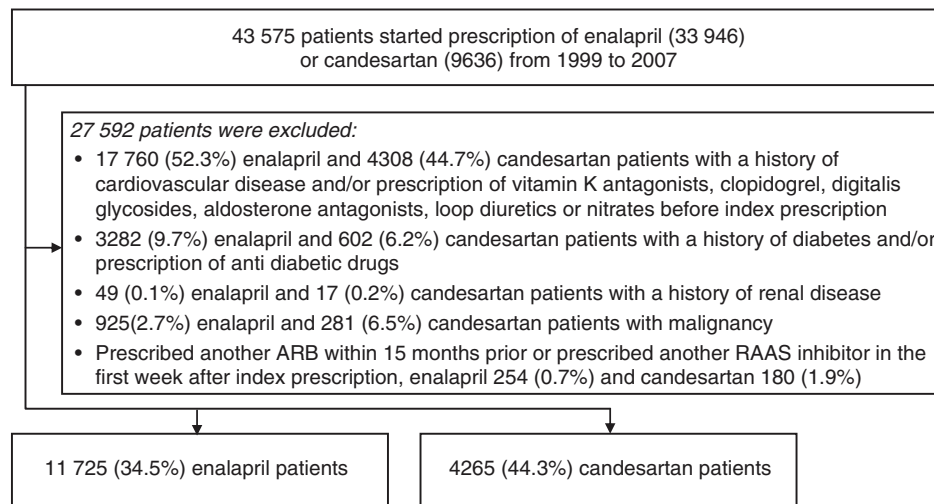


Figure 1. Patient flow.

Table 1. Baseline data from 15 990 hypertensive patients without previous cardiovascular disease and diabetes

Variable	Unmatched			Propensity score matched		
	Enalapril (n = 11 725)	Candesartan (n = 4265)	P-value	Enalapril (n = 1111)	Candesartan (n = 1111)	P-value
Age (years)	61.0 (12.1)	60.0 (11.6)	<0.01	59.6 (10.8)	59.7 (10.7)	0.81
Women, n (%)	6216 (53)	2431 (57)	<0.01	582 (52)	583 (53)	1.00
Body mass index (kg m <sup>-2</sup> )	29.2 (5.3)	28.9 (5.2)	0.10	28.8 (4.8)	29.5 (5.2)	0.04
Systolic blood pressure (mm Hg)	163.3 (19.1)	162.0 (19.2)	<0.01	161.5 (18.7)	161.7 (18.3)	0.80
Diastolic blood pressure (mm Hg)	91.8 (10.6)	91.8 (10.4)	0.94	92.2 (10.2)	92.1 (10.2)	0.71
Total cholesterol (mmol l <sup>-1</sup> )	5.9 (1.0)	5.8 (1.0)	0.11	5.9 (1.0)	5.9 (1.0)	0.88
LDL cholesterol (mmol l <sup>-1</sup> )	3.6 (0.8)	3.6 (0.8)	0.90	3.6 (0.8)	3.6 (0.8)	0.79
HDL cholesterol (mmol l <sup>-1</sup> )	1.4 (0.3)	1.4 (0.3)	0.92	1.4 (0.3)	1.3 (0.3)	<0.01
Triglycerides (mmol l <sup>-1</sup> )	1.6 (0.8)	1.6 (0.8)	0.37	1.6 (0.7)	1.7 (0.8)	0.12
Glucose (mmol l <sup>-1</sup> )	5.4 (1.1)	5.3 (1.1)	<0.01	5.3 (1.3)	5.3 (1.3)	0.63
HbA1c (%)	4.9 (0.7)	4.7 (0.5)	<0.01	4.7 (0.5)	4.9 (0.7)	<0.01
Serum creatinine (μmol l <sup>-1</sup> )	79.6 (16.7)	82.3 (16.2)	<0.01	81.4 (16.1)	82.0 (16.2)	0.41
Potassium (mmol l <sup>-1</sup> )	4.1 (0.3)	4.1 (0.3)	0.12	4.1 (0.3)	4.1 (0.3)	0.57
Thiazides, n (%)	2082 (18)	525 (12)	<0.01	204 (18)	197 (18)	0.74
Calcium channel blockers <sup>a</sup> , n (%)	1181 (10)	555 (13)	<0.01	172 (15)	181 (16)	0.64
Beta blockers, n (%)	2855 (24)	1050 (25)	0.74	351 (32)	366 (33)	0.52
Statins, n (%)	749 (6)	290 (7)	0.37	137 (12)	137 (12)	0.95
Socio-economic status <sup>b</sup> (low/medium/high)	35/33/32	31/32/37	<0.01	33/29/39	32/30/38	0.76
Percentage of patients hospitalized for any reason <sup>c</sup>	10.6%	11.1%				
Number of visits in primary care <sup>c</sup>	2.0	2.0				
Total number of diagnoses set (100 patients year <sup>-1</sup> ) <sup>c</sup>	196.3	196.7				

Abbreviations: HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein. The numbers in brackets represents s.d., where no other description is given. <sup>a</sup>Dihydropyridine substances. <sup>b</sup>Educational level. <sup>c</sup>Within 15 months before the start of study.

females (-4%), had a higher systolic blood pressure (+0.1 mm Hg), higher blood glucose (+0.1 mmol l<sup>-1</sup>), higher HbA1c (+0.2%) and lower serum creatinine (2.6 μmol l<sup>-1</sup>). Concomitant treatments differed by the enalapril group being more frequently treated with thiazides (+6%) and less frequently with calcium channel blockers (-3%). Patients treated with enalapril had a generalized lower socio-economic status. There were no observed differences with regard to health care utilization (hospitalizations and length of stay, number of primary care visits and number of new diagnoses) between the two groups within 15 months from the start of the study. The proportion of included

patients per year, from 1999 to 2007, showed a larger proportion of enalapril patients included at the end (2005–2007) of the observation period (data in Supplementary Table S3).

#### Follow-up

The observation period comprised a total of 36 482 patient-years: 23 429 patient-years of enalapril treatment and 13 053 patient-years of candesartan treatment. The mean time (s.d.) of follow-up was 1.84 (1.97) years in the enalapril and 2.85 (2.31) years in the candesartan group.

There was no difference in the number of visits to primary care and laboratory/blood samples taken between the two groups during the first 2 years of the study (data in Supplementary Tables S4 And 5). Weight at baseline and weight during follow-up was similar in the groups (data in Supplementary Figure S1). During the observation period, 38.7% ( $n=4538$ ) patients were discontinued from the enalapril-treated group and 27.1% ( $n=1157$ ) from the candesartan group. Reasons for discontinuations were death: 2.6% ( $n=305$ ) vs 2.5% ( $n=107$ ), switch to other C09-drugs 20.0% ( $n=2345$ ) vs 8.7% ( $n=372$ ) or cessation of study drug prescription 16.1% ( $n=1888$ ) vs 15.9% ( $n=678$ ) in the enalapril group and the candesartan group, respectively.

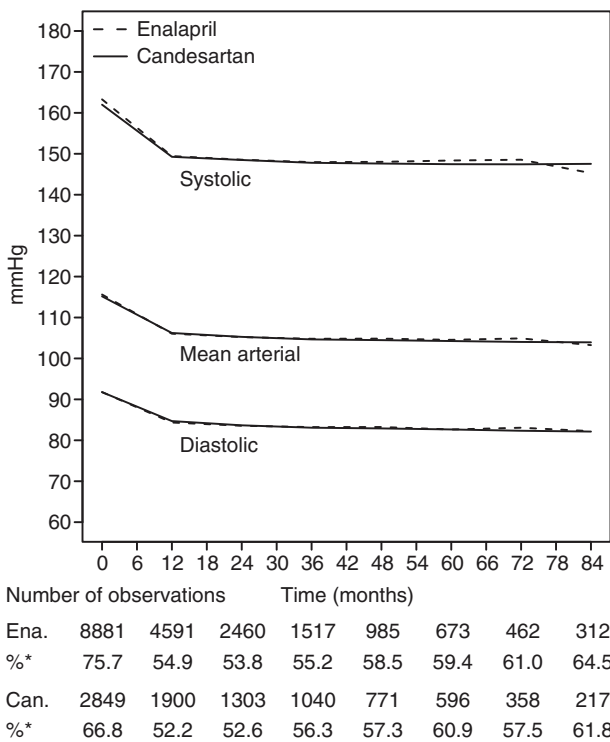
**On-treatment blood pressures**

The initiation of enalapril or candesartan was followed by a substantial blood pressure reduction, with no difference in blood pressure between the two treatment groups (Figure 2). The proportion of patients with blood pressure recordings was similar in both the treatment groups after 1 year of treatment.

**Incidence of new diagnosed diabetes**

A total of 991 subjects with a new diagnosis of diabetes were recorded during the observation period. The incidence rate was 0.074 per 100 patient-years and 0.066 per patient-years in the enalapril and candesartan group, respectively. The unadjusted risk of a new diagnosis of diabetes was lower (HR 0.77, 95% CI 0.66–0.90,  $P<0.01$ ) in patients treated with candesartan compared with those with enalapril (Figure 3). This risk remained lower in candesartan patients after adjusting for age, gender, index year and socio-economic status, (HR 0.81, 95% CI 0.69–0.96,  $P=0.01$ ).

Results of the additional sensitivity analyses with adjustments for baseline HbA1c, blood glucose and body mass index were consistent with the results from the main analysis for diabetes.



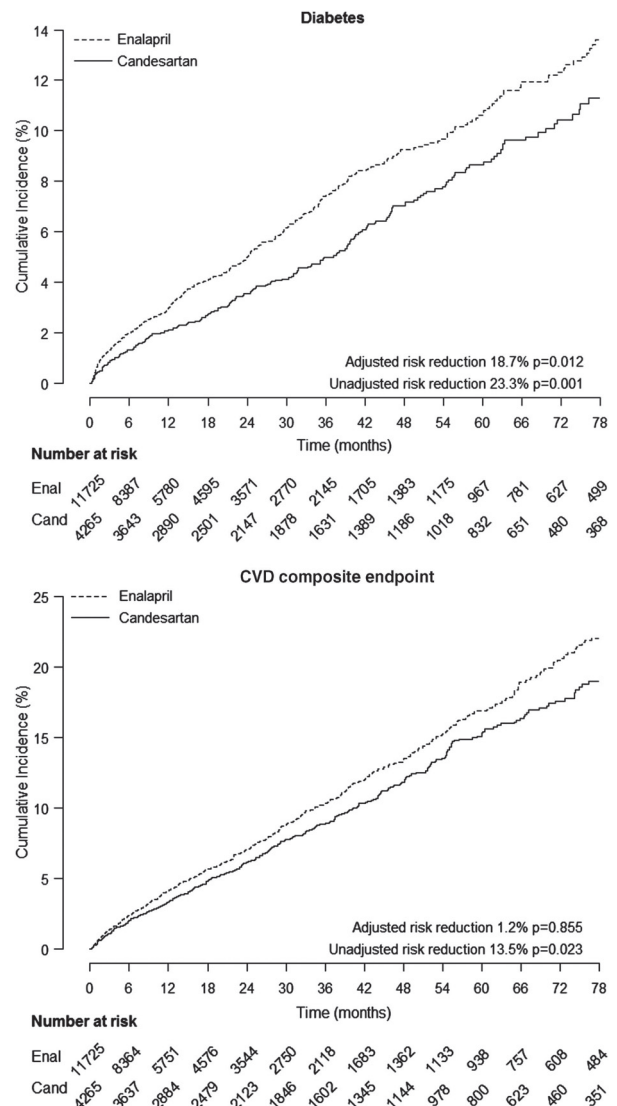
**Figure 2.** Blood pressure during follow-up. %\*Percentage of blood pressure reading among patients at risk. Ena, enalapril; Can, candesartan.

The same result was also observed when diabetes diagnoses set within 6 and 12 months after the start of the study were excluded (Table 2). Few patients had high baseline HbA1c ( $>7\%$ ; 0.14% vs 0.02%) or blood glucose ( $>7\text{ mmol l}^{-1}$ , 3.99% vs 2.49%;  $>10\text{ mmol l}^{-1}$ , 0.37% vs 0.28%) values in the enalapril and candesartan groups. When these patients were excluded from the analyses, the results were also consistent with the main analysis (data in Supplementary Table S4).

The patient characteristics in the two groups after the propensity score matching are summarized in Table 1. In propensity score-matched analyses, candesartan patients had a lower risk of diabetes development, HR 0.63 (95% CI 0.42–0.96,  $P=0.03$ ).

**Incidence of CVD**

During the study, 785 CVD events occurred in the enalapril group and 375 in the candesartan group. The unadjusted risk of CVD was lower in candesartan patients than in enalapril patients (HR 0.87, 95% CI 0.76–0.98,  $P=0.02$ ; Figure 3). When adjusting for covariates (age, gender, index year, socio-economic status), the risk was similar in the two groups (HR 0.99, 95% CI 0.87–1.13,



**Figure 3.** Kaplan–Meier curves for diabetes and composite CVD endpoint. Ena, enalapril; Can, candesartan.

**Table 2.** Effect of additional adjustment and different analysis methods on clinical outcomes obtained from primary care journals and Swedish national discharge and death registers

	Number of patients		HR, new-onset diabetes	HR, CVD
	Enalapril, n	Candesartan, n		
Unadjusted	11 725	4265	0.77 (95% CI 0.66–0.90)	0.87 (95% CI 0.76–0.98)
Primary adjusted results <sup>a</sup>	11 725	4265	0.81 (95% CI 0.69–0.96)	0.99 (95% CI 0.87–1.13)
+ systolic BP (Multiple imputed values) <sup>b</sup>	11 725	4265	0.80 (95% CI 0.68–0.94)	0.92 (95% CI 0.81–1.05)
+ systolic BP (available values) <sup>b</sup>	8881	2849	0.79 (95% CI 0.65–0.96)	0.97 (95% CI 0.83–1.13)
+ HbA1c <sup>b</sup>	1151	428	0.79 (95% CI 0.58–1.07)	–
+ blood glucose <sup>b</sup>	7338	2256	0.78 (95% CI 0.64–0.96)	–
+ BMI <sup>b</sup>	2896	772	0.86 (95% CI 0.97–1.15)	–
Excluding patients diagnosed within 6 months after the start of the study <sup>c</sup>	11 520	4212	0.87 (95% CI 0.72–1.05)	0.98 (95% CI 0.86–1.12)
Excluding patients diagnosed within 12 months after the start of the study <sup>c</sup>	11 443	4185	0.88 (95% CI 0.72–1.10)	0.97 (95% CI 0.85–1.11)
Propensity score analysis <sup>d</sup>	1111	1111	0.63 (95% CI 0.42–0.96)	0.88 (95% CI 0.56–1.24)

Abbreviations: BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; HR, hazard ratio. <sup>a</sup>Adjusted for age, gender, index year and socio-economic status. <sup>b</sup>Added adjustments to primary adjustments. <sup>c</sup>Primary adjustments. <sup>d</sup>Matched for gender, age, index year, systolic blood pressure, total cholesterol, blood glucose, socio-economic status, beta blockers, statins, calcium antagonists and thiazides.

$P=0.86$ ). Similar results were observed when multiple imputations were performed for systolic blood pressure.

In the 2222 patients in the propensity score-matched analysis, the HR of CVD was 0.83 (95% CI 0.56–1.24,  $P=0.37$ ).

Additional sensitivity analyses were performed in order to explore the effect of variations in the proportion of included patients per year in addition to adjustment for inclusion year. The results with an adjusted HR of 1.00 (95% CI 0.87–1.15,  $P=1.00$ ) for the cohort of included patients from 1999 until 2005 supported the main results.

#### Treatment patterns

Both enalapril and candesartan were prescribed accordingly to the prescribing recommendations for hypertension. The enalapril group generally started with 5 mg (25.5%) or 10 mg (35.8%) and patients were up-titrated to 10 mg (31.0%) and 20 mg (36.5%) during the first 3 years of treatment. The use of fixed combination tablets (enalapril 20 mg/hydrochlorothiazide 12.5 mg) rose from 9.2% until 13.4% during the study period.

The candesartan group started mainly with 4 mg (27.6%) or 8 mg (50.3%) with an up-titration during the first 12 months of treatment to 43.2% for use of the 8 mg tablet and 20.4% for the 16 mg tablet. After 3 years of treatment, the patients treated with candesartan were mainly treated with 8 mg (35.3%), 16 mg (23.3%) or 16 mg/12.5 mg (24.1%) tablets.

The use of other antihypertensive medications increased in both groups during follow-up. Thiazides (both separate and in fixed combination tablets) were used more frequently in the enalapril group initially. This changed during follow-up; after 1 year on treatment, candesartan patients were more frequently treated with thiazides (34% vs 24%), and the difference in proportion of thiazides-treated patients between the two groups continued to increase during follow-up (data in Supplementary Figure S2). More calcium channel blockers and beta blockers were added in the enalapril group.

## DISCUSSION

### Primary observations

In this comparative effectiveness study of 15 990 hypertension patients without CVD or diabetes in real-life primary care, initiation

of enalapril or candesartan was followed by a substantial blood pressure reduction, with no difference in blood pressure between the two treatment groups during the follow-up period. Candesartan patients had, however, a lower risk of new diagnosed diabetes compared with enalapril patients. These results were consistent across different analyses and subpopulations (data in Supplementary Figure S3). No difference in CVD risk was observed between the two groups.

### Interpretation with reference to other studies

The results of this study suggest that there is a risk reduction of new-onset diabetes with candesartan compared with enalapril in the treatment of hypertension. Both ACEi and ARBs have in previous studies shown a reduction in new onset of diabetes.<sup>1–4</sup> A reduction in new onset of diabetes in the ARB group compared with the ACEi group may be supported by previous observations.<sup>5</sup> Lack of activation of parts of the PPAR system with ACEi treatment, and thus less stimulation of glucose activation, has been postulated as an explanation for potential differences vs ARB in the prevention of new onset of diabetes.<sup>6</sup> Candesartan has a tight and long-lasting binding to the AT type 1 receptor.<sup>23</sup> The potential to prevent new-onset diabetes may therefore be explained by a more effective blockade of AT type I receptors and the subsequent development of vascular insulin resistance and impaired endothelial nitric oxide-mediated relaxation.<sup>7</sup>

During the study, there was no difference between the two treatments in protection for CVD. This finding is in line with results from randomized controlled studies comparing the CVD-protective effect of ACEi and ARB treatments.<sup>8,9</sup> Differences with regard to new-onset diabetes rates during the study may not be expected to affect CVD incidence due to the relatively short study duration. The treatment period for patients treated with enalapril was generally shorter, indicating a lower tolerability for enalapril compared with candesartan. These findings, indicating a lower tolerability of ACEi treatment, are in agreement with findings from other real-life and randomized controlled studies.<sup>23–27</sup>

### Strengths and limitations

The present study was performed using primary care data from primary care centers which represented 7% of all primary care

centers in Sweden. High-quality national data on hospitalizations, prescribed drugs and causes of death were also included. This provides a representative selection of patients and a more or less complete long-term follow-up of newly diagnosed diabetes and major cardiovascular events.

#### Potential effect of unmeasured confounders

As commonly in non-randomized studies of the effectiveness of drug treatment, it cannot be excluded that residual confound may have influenced the findings. In-depth understanding for why physicians choose enalapril or candesartan for treatment for hypertension can only be explored by quality interviews with the prescribing physicians, data we unfortunately do not have access to in this study. Data on smoking and physical activity were missing for the majority of patients and was therefore not included in the analyses. The general socio-economic status was lower in the enalapril group, and potentially more patients could be expected to smoke in this group or have a different physical activity profile. The difference in socio-economic status is, however, adjusted for in all the analyses. We did not observe a difference between the two groups with regard to the proportions of patients with chronic obstructive pulmonary disease and or use of chronic obstructive pulmonary disease medications, which is closely related to smoking. Nor did we see differences in mean weight during follow-up (data in Supplementary Figure S3). In consideration of the possible impact of residual confounding, it should be recognized that Sweden has a tax-funded healthcare system with equal access to health-care services and drugs, thus choice of treatment and patient follow-up should be primarily based on clinical data and not on non-medical reasons. We did not observe differences in how the patients were treated and followed up before and after the start of study medication in the recorded data.

#### Missing blood pressure values

One of the limitations with this method is missing data in the electronic patient primary care journals. Blood pressure recordings were registered in 72% of all the patients at baseline. The enalapril group had a slightly higher baseline systolic blood pressure compared with the candesartan group. However, analysis with multiple imputations for missing systolic blood pressure and analysis with adjustment for available systolic blood pressures gave the same results (Table 2).

#### Opportunistic diagnosis

A potential explanation of the finding of more new diagnoses of diabetes in the enalapril group could be 'opportunistic diagnosis' due to a potential increased number of patient visits to primary care in this group who had a higher non-CVD burden. However, the frequency of primary care visits, diagnoses, laboratory/blood samples data and hospitalizations before the start of the study did not differ markedly between the two groups, suggesting similar needs for medical consultations at baseline. We did not observe any major difference in the number of annual primary care visits or blood samples taken between the two treatment groups during follow-up (data in Supplementary Tables S5 and S6). The finding of increased number of diabetes diagnoses in the enalapril group did not follow the general trend regarding other diagnoses during the observation period as the number of other diagnoses made during the study was higher in the candesartan group. This does not support the possibility of a general higher disease burden in the enalapril group (data in Supplementary Table S7).

#### Risk of the differential exclusion of patients

Enalapril and candesartan have the same prescribing indications in Sweden; both are indicated for hypertension and heart failure

but not for renal diseases. However, the ACEi were developed before the ARB class and thus gained hard end point documentation and CVD indications (heart failure, myocardial infarction) earlier. More patients (11.2%) were excluded for earlier diabetes and CVD in the enalapril group. Patient records in primary care were searched for chronic kidney disease, diabetes and CVD diagnoses and drugs up to 5–6 years before inclusion. The same diagnoses were also searched for in the National Patient Register, which has a national coverage since 1987.<sup>12</sup> The combination of these two search techniques should therefore have lowered the risk of undetected diabetes and CVD prevalence at baseline.

#### Difference in treatment practice over time

When including patients over a long time span, an important potential confounding factor could have been variations in hypertensive treatment over time, favoring inclusion either in the enalapril or candesartan group. Alterations in the Swedish reimbursement system for the use of RAAS (renin-angiotensin-aldosterone system)-inhibiting drugs for hypertension in 2008 are an example. Qualifications for reimbursement for hypertension from this date required that patients should start with an ACEi and ARBs should be prescribed as a second-line treatment for patients with side effects on ACEi treatment or as an add-on therapy (heart failure). These requirements were implemented earlier in some areas of Sweden. The annual frequency of inclusion to the enalapril or candesartan group from 1999 to 2007 reflects these changes; by a relatively higher use of enalapril from 2005 (data in Supplementary Table S3). In order to minimize the possible effects of temporal changes, index year (start of treatment) was included as covariate/adjustment in all the analyses. The same results were observed when we excluded patients included in 2005–2007 from the study.

The study had a follow-up time of mean (s.d.) 2.11 (2.11) years. There was a major difference in follow-up time between the two groups, the enalapril group with a mean (s.d.) of 1.84 (1.97) years and a mean 2.85 (2.31) years in the candesartan group. This difference can partly be explained by a larger portion of enalapril patients included at the end of the observation period. Nevertheless, when excluding patients included during the last 3 years of the observation period, the enalapril patients still have, in general, a shorter median follow-up period (–0.84 years) caused by higher number of patients who switched to other C 09 drugs or ending their enalapril treatment.

#### Perspectives

Our study method can be used to study existing treatments, providing results faster than performing a prospective randomized clinical trial and at a moderate cost. Sweden offers the unique combination of a wide use of similar electronic patient record systems in primary care and a long tradition with nationwide hospitalization and cause of death registers. This provides the unique opportunity to study differences between treatments, which are not possible to assess in randomized clinical trials.

The results of this study suggest that there is a risk reduction of new-onset diabetes with candesartan compared with enalapril in the primary treatment of hypertension, while the two treatments provide similar protection for CVD. Patients treated with enalapril had a shorter treatment period, indicating a lower tolerability for enalapril compared with candesartan. The results of this retrospective study should be confirmed, however, in prospective studies before any definitive conclusions are made.

#### CONFLICT OF INTEREST

LPH is enrolled at the PhD School of the University of Oslo, Faculty of Medicine. LPH, NH and JB are employed by AstraZeneca. AstraZeneca sells candesartan in many markets. Candesartan has lost patent protection. MT is employed by an independent

statistical consultant company, Statisticon, for which AZ is a client. J Stålhammar has received honoraria for lecturing/consulting and other research support from AZ. J Sundström has received honoraria for advisory board participation from AZ. DR has received honoraria for lecturing/consulting and other research support from AZ, Boehringer Ingelheim, Pfizer and Bayer. SEK has received honoraria for lecturing/consulting and other research support from AZ, Bayer, Medtronic, MSD, Pronova, Serodus and Takeda.

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