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FROM STATIN EFFICACY TO EVERYDAY EFFECTIVENESS: STUDYING THE GAP IN BETWEEN

Päivi Ruokoniemi

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To my loved ones

ABSTRACT

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From statin efficacy to everyday effectiveness: Studying the gap in between.

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Statins are indicated for preventing cardiovascular disease events. Patients with diabetes have a risk of major cardiovascular events double the risk of their peers without diabetes. Thus, clinical treatment guidelines recommend statins for the management of diabetic dyslipidemia.

The evidence base for statin use in cardiovascular disease derives from the randomised controlled statin trials designed to prove statin efficacy under ideal conditions, among a homogenous study population meeting strict trial eligibility criteria. This thesis was implemented as four pharmacoepidemiological statin studies using register data on real-world statin users. The overall purpose was to evaluate the trends, patterns and effectiveness of statin use in everyday life. More specifically, nationwide secular trends in statin use in Finland were analysed, especially among patient groups which had been underrepresented in the statin trials. Furthermore, the benchmarking statin trials in diabetes, the Heart Protection Study and the Collaborative Atorvastatin Diabetes Study, were evaluated for their representativeness for real-world diabetes care with the emphasis placed on adherence to statin use. The association between good adherence and the incidence of major cardiovascular events in the real-world was further investigated in diabetes.

These studies demonstrate that statin initiations increased from 1995 to 2005 in Finland. The increase was most pronounced among those aged at least 75 years and was observed already before the publication of rigorous trial data conducted in elderly subjects. Thus, statins seem to have been initiated in clinical practice also going beyond the strict trial eligibility criteria. Nonetheless, low adherence to statin use among the real-world patients with diabetes was found not only to limit the representativeness of the trials for clinical care but also to attenuate in all likelihood their benefits in the real-world. In fact, good adherence to statin use was found to associate with a decreased risk for major cardiovascular events in patients with diabetes.

In conclusion, these studies highlight the importance of good adherence to statin use in clinical practice in order to obtain the full therapeutic value demonstrated in the statin trials. Simply increasing the number of statin users will not alone suffice in sharing our common resources appropriately.

Keywords: adherence, diabetes, randomised controlled trials, pharmacoepidemiology, statins

TIIVISTELMÄ

Päivi Ruokoniemi
Statiinien teho ja arkielämän vaikuttavuus: Tutkimus raja-alueesta niiden välissä.

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Statiinien käyttöaihe on sydän- ja verisuonisairaustapahtumien esto. Diabetespotilailla on kaksinkertainen riski saada merkittävä sydän- tai verisuonisairaustapahtuma diabetesta sairastamattomiin verrattuna. Siksi hoitosuositukset suosittavat statiineja diabeettisen dyslipidemian hoitoon.

Statiinien käyttöä sydän- ja verisuonisairaustapahtumien estossa tukeva tutkimusnäyttö perustuu satunnaistettuihin, kontrolloituihin hoitotutkimuksiin, jotka on suunniteltu osoittamaan statiinien teho optimaalisissa olosuhteissa, homogeenisen, tiukat sisäänotto-kriteerit täyttävän tutkimuspopulaation joukossa. Tämä väitöskirja sisältää neljä lääke-epidemiologista tutkimusta, joissa käytettiin rekisteritietoja arkielämän statiinikäyttäjistä. Tutkimuksen tavoitteena oli tutkia statiinien käytön trendejä, tapoja ja vaikuttavuutta arkielämässä. Statiinien käytössä tapahtuneita ajallisia muutoksia Suomessa analysoitiin erityisesti niissä potilasryhmissä, jotka olivat aliedustettuina statiinihoitotutkimuksissa. Lisäksi merkittävien statiinihoitotutkimusten (Heart Protection Study ja Collaborative Atorvastatin Diabetes Study) edustavuutta arvioitiin käytännön diabeteshoidon kannalta kiinnittämällä erityistä huomiota statiinihoitoon sitoutumiseen. Ohella tutkittiin hyvän statiinihoitoon sitoutumisen ja merkittävien sydän- ja verisuonisairaustapahtumien ilmaantumisen välistä yhteyttä arkielämän diabetespotilailla.

Väitöskirjatutkimus osoittaa, että statiinihoitojen aloitukset Suomessa lisääntyivät vuodesta 1995 vuoteen 2005, mikä havaittiin erityisesti 75-vuotiaiden ja sitä iäkkäämpien keskuudessa jo ennen heitä koskevan tutkimusnäytön julkaisemista. Vaikuttaakin siltä, että statiinihoitoja aloitetaan arkielämässä statiinihoitotutkimusten tiukkojen sisäänotto-kriteereiden sanelematta. Väitöskirjatutkimus kuitenkin osoitti, että arkielämän diabetes-potilaiden heikompi statiinihoitoon sitoutuminen ei pelkästään rajoittanut arvioitujen hoitotutkimusten edustavuutta, vaan todennäköisesti myös laimentaa statiinihoidosta saatavaa hyötyä. Väitöskirjatyössä nimittäin havaittiin, että diabetespotilailla hyvään statiinihoitoon sitoutumiseen liittyy pienempi sydän- ja verisuonisairaustapahtumien riski.

Yhteenvetona todetaan, että tämä väitöskirjatyö osoittaa hyvän statiinihoitoon sitoutumisen merkityksen tavoiteltaessa kliinisissä tutkimuksissa osoitettua statiinien hoidollista arvoa arkielämässä. Statiinien käyttäjämäärien kasvattaminen ei yksinään riitä kohdennettaessa yhteisiä voimavarojamme asianmukaisesti.

Avainsanat: diabetes, hoitoon sitoutuminen, lääke-epidemiologia, satunnaistettu, kontrolloitu hoitotutkimus, statiinit

TABLE OF CONTENTS

ABBREVIATIONS

AFCAPS/TexCAPS*	Air Force/Texas Coronary Atherosclerosis Prevention Study
AP	angina pectoris
ASCOT-LLA*	Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CARDS*	Collaborative Atorvastatin Diabetes Study
CARE*	Cholesterol and Recurrent Events
CHD	coronary heart disease
CI	confidence interval
CK	creatinine kinase
CVD	cardiovascular disease
DDD	Defined Daily Dose
DM	diabetes mellitus
HbA1c	glycated haemoglobin
HDL	high density lipoprotein
HMG-CoA	hydroxymethylglutarylcoenzyme A
HPS*	Heart Protection Study
HPS (DM)*	A subanalysis of the Heart protection Study on DM
HR	hazard ratio
HT	hypertension
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
JUPITER*	Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
LDL	low dense lipoprotein
LIPID*	Long–term Intervention with Pravastatin in Ischaemic Disease
LLD	lipid-lowering drug
LIPS*	Lescol Intervention Prevention Study
mAb	monoclonal antibody
MCE	major coronary event
MI	myocardial infarction
MPR	medication possession ratio
NA	not available
NCD	non-communicable disease
OATP1B1	organic anion transporting polypeptide 1B1
OR	odds ratio
PAD	peripheral arterial disease
PDC	proportion of days covered
PROSPER*	Prospective Study of Pravastatin in the Elderly at Risk

PROVE-IT*	Pravastatin or Atorvastatin Evaluation and Infection Therapy Study
RCT	randomised controlled trial
Ref	reference
RR	rate ratio/relative risk
RRR	relative risk reduction
SHARP*	Study of Heart and Renal Protection
SII	Social Insurance Institution
SPARCL*	Stroke Prevention by Aggressive Reduction in Cholesterol Levels
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TNT*	Treating to New Targets Study
TC	total cholesterol
UKPDS	United Kingdom Prospective Diabetes Study
WHO	World Health Organization
WOSCOPS*	West of Scotland Coronary Prevention Study
4S*	Scandinavian Simvastatin Survival Study

*a randomised controlled statin trial

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications referred to in the text by their Roman numerals.

I Ruokoniemi P, Helin-Salmivaara A, Klaukka T, Neuvonen PJ, Huupponen R. Shift of statin use towards the elderly in 1995-2005: a nation-wide register study in Finland. Br J Clin Pharmacol. 2008 Sep;66(3):405-10.

II Ruokoniemi P, Sund R, Arffman M, Helin-Salmivaara A, Huupponen R, Keskimäki I, Vehko T, Korhonen MJ. Are statin trials in diabetes representative of real-world diabetes care: a population-based study on statin initiators in Finland. BMJ Open 2014;4:e005402. doi:10.1136/bmjopen-2014-005402

III Ruokoniemi P*, Korhonen MJ*, Helin-Salmivaara A, Lavikainen P, Jula A, Junnila SYT, Kettunen R, Huupponen R. Statin Adherence and the risk of major coronary events in patients with diabetes. A nested case-control study. Br J Clin Pharmacol. 2011 May;71(5):766-76.

IV Korhonen MJ, Ruokoniemi P, Ilomäki J, Helin-Salmivaara A, Huupponen R. Adherence to statin therapy and the incidence of ischemic stroke in patients with diabetes. Manuscript to be submitted.

*authors contributed equally

1 INTRODUCTION

The rational use of drugs in clinical practice requires knowledge of their benefits and risks for a given indication. At the time of marketing authorization this knowledge derives from the randomised controlled trials (RCTs) designed to demonstrate the drug efficacy and safety under ideal conditions. However, many questions important in the medical decision making in clinical practice remain unanswered at the time of drug approval.

The RCTs apply strict inclusion and exclusion criteria when recruiting trial participants in order to gather a homogenous trial population. This is considered essential for reducing noise and assuring the internal validity of the trial findings. Nonetheless, the eligibility criteria may decrease the representativeness of the trial participants for the relevant patient population in clinical practice. Patients with diverse demographical characteristics, with multiple comorbidities, with varying prognoses or with less than optimal adherence to drugs, may be underrepresented in the clinical trials. As deviations in representativeness may limit the extent to which the expected drug effects are achieved in clinical practice, the effectiveness of drugs can only be investigated after drug approval.

Statins are one of the most commonly used drugs worldwide. They were first launched during the late 1980´s but it was only after the publication of the landmark RCTs in the late 90´s, the Scandinavian Simvastatin Survival Study (4S) (Scandinavian Simvastatin Survival Study Group 1994), the West of Scotland Coronary Prevention Study (Shepherd *et al.* 1995) and the Cholesterol and Recurrent Events study (Sacks *et al.*1996), when the consumption of statins rapidly increased all around the world. Pfizer´s atorvastatin with the tradename Lipitor® became the best-selling drug in the history of the pharmaceutical industry. Subsequently, there rose a need for understanding and improving statin utilisation across health care systems. This stimulated the need for pharmacoepidemiological statin studies.

The World Health Organization (WHO) defines pharmacoepidemiology as “the study of the use and effects/side-effects of drugs in large numbers of people with the purpose of supporting the rational and cost-effective use of drugs in clinical care of patients” (WHO 2003). Pharmacoepidemiology combines the knowledge of drug effects from clinical pharmacology, i.e. the pharmacokinetic and pharmacodynamic profiles of drugs, with epidemiological study methods (Strom 2002, Ness *et al.* 2009). Pharmacoepidemiological studies are a key component of the post authorization pharmacovigilance activities (ICH 2004).

There are ~ 350 million patients with diabetes in the world today and the prevalence is still increasing. Diabetes is a heterogeneous disease which confers an increased risk of encountering cardiovascular complications. According to the WHO, cardiovascular causes, mainly ischemic heart disease and stroke, account for 50% of all deaths in

patients with diabetes. Diabetes doubles the risk of coronary heart disease and ischemic stroke as compared to the non-diabetic state (Emerging Risk Factors Collaboration 2010). Therefore, patients with diabetes are recommended not only to follow a healthy life style but also to use several drugs, including statins, in order to reduce their risk of encountering cardiovascular events.

The evidence base for statin use in diabetes derives from meta-analyses and individual RCTs confirming the benefits of statins under ideal conditions. Very little data are available on the expected benefits attainable with statins in real-world clinical diabetes care.

The purpose of this thesis was to analyze nationwide secular trends, patterns and effectiveness of statin use in Finland with epidemiological data. Simultaneously, the aim was to elucidate the factors impacting on translating the benefit demonstrated for statins in the RCTs into a real-world setting. On a more general level, this thesis focuses on themes that are best described with the words of Sir Austin Bradford Hill, an English epidemiologist and a pioneer for randomised clinical trials, who stated in 1965: "All scientific work is incomplete - whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. This does not confer on us to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time."

2 REVIEW OF THE LITERATURE

2.1 Cardiovascular diseases

2.1.1 Impact on public health

Cardiovascular diseases (CVDs) are a heterogeneous group of disorders affecting the heart and blood vessels. Established CVD may manifest as ischaemic heart disease, cerebrovascular disease or as diseases of the aorta and arteries, such as hypertension and peripheral arterial disease (PAD) (WHO 2011a). The other forms of CVD include rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism (available at www.who.int). The atherosclerotic coronary heart disease (CHD) and cerebrovascular disease account for the majority of CVD deaths (Figure 2.1).

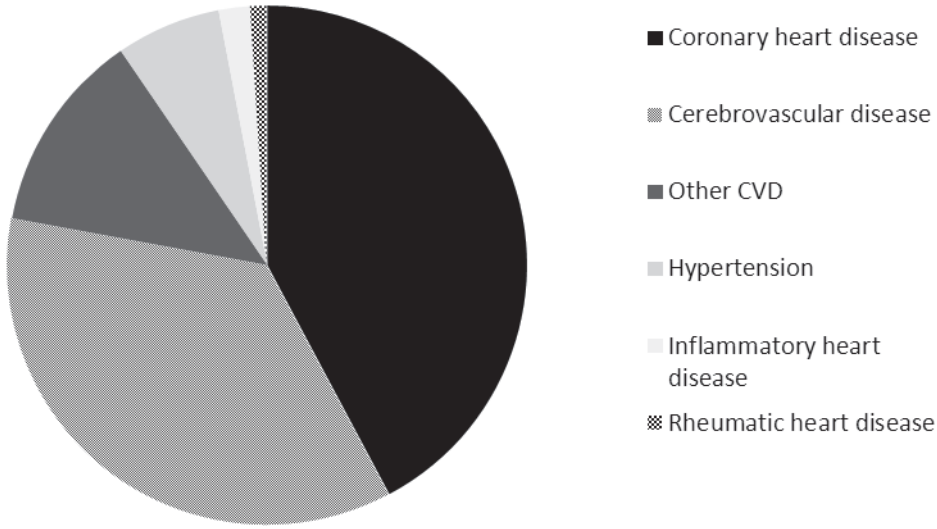

Figure 2.1. Global distribution of CVD deaths due to heart attacks, strokes and other types of CVD (based on WHO 2011a).

CVD is the leading cause of premature, non-communicable disease (NCD) deaths globally. In 2008, CVD was responsible for 39% of all NCD deaths among persons under the age of 70 (WHO 2011b) while the second leading cause, cancer, accounted for 27% of deaths. Of CVD related deaths, 60-80% occur in the low and middle income countries where the prevalence of established CVD risk factors is high (Marmot and Elliot 2005, WHO 2011b).

In many developed countries, such as the USA and many northern and western European countries, the mortality, incidence, and case fatality of CHD have been declining over the last 20 to 30 years (Ergin *et al.* 2004, Tunstall-Pedoe *et al.* 1999). This trend has also been observed in Finland, a country which once had the highest CHD mortality rates in the world (Kattainen *et al.* 2006). Simultaneously, CHD in Finland has transformed from a disease of middle aged men into one affecting elderly women (Kattainen *et al.* 2006). The decline in CHD mortality in Finland reflects the reductions occurring in CHD risk factors such as serum total cholesterol, blood pressure and smoking at the population level (Vartiainen *et al.* 2010).

2.1.2 Cardiovascular risk factors and basic pathology

The currently favoured theory to explain the pathology of atherosclerotic CVD is that based on the response-to-injury hypothesis, which best accounts for the various risk factors for atherosclerotic CVD (Kumran *et al.* 1997). The basic features of the hypothesis are as follows: the chronic endothelial injury and dysfunction of the blood vessels, as well as increased insudation of lipoproteins, mainly of low density lipoprotein (LDL), into the vessel wall trigger various cellular interactions, including an inflammatory cellular response, smooth muscle cell proliferation and an increased formation of collagen and other components of the extracellular matrix (Kumran *et al.* 1997, Legein *et al.* 2013, Hajjar *et al.* 2013). This results in the formation of a fibrofatty atheroma, the pre-stage of the fibrous, atheromatous plaque, commonly recognized as the hallmark of atherosclerosis. The oxidative modification of LDL particles is thought to be an essential step in the early formation of the atheroma (Weber and Noels 2011, Hajjar *et al.* 2013).

Atheromas cause morbidity and mortality by obstructing luminal blood flow, leading to the rupture of atheromatous plaques with subsequent thrombosis, and by facilitating aneurysmal formation and also making vessel rupture more likely (Legein *et al.* 2013, Rudolf and Lewandrowski 2014). The rupture of the atheromatous plaque and thrombosis manifest as the most common forms of CVD: acute coronary syndrome, myocardial infarction (MI) or stroke (Weber and Noels 2011). However, as an etiological factor, the role of the atheromatous plaque is grater in acute coronary events than it is in stroke accounting for 75-95% of acute MIs compared to 15-48% of strokes (Soler and Ruiz 2010). The latter is considered as being a more heterogeneous disease with the etiological factor remaining unknown in 38% of cases (Soler and Ruiz 2010). Furthermore, stroke is classified into two separate entities, ischemic stroke and haemorrhagic stroke, with ischemic stroke accounting for 90% of all cases (Andersen *et al.* 2009).

Modifiable, behavioural risk factors, such as smoking, physical inactivity and unhealthy diet are believed to account for 80% of all atherosclerotic coronary heart disease (CHD) and cerebrovascular disease (WHO 2011b). These behavioural factors may present in individuals as major acquired, established risk factors for atherosclerotic CVD, i.e. dyslipidemia, hypertension, diabetes and obesity. These are recognized as established risk factors based on the large amount of data emphasising their significance in the aetiology of CVD as they are known to be crucial due to their high prevalence in (western) populations, to their modifiable nature and to the strong association between their presence and the risk of CVD events (Marmot and Elliot 2005). The various factors associating with the risk for CVD events are presented in Table 2.1.

Table 2.1 Factors associating with the risk of CVD events (based on Marmot and Elliot 2005, Patra *et al.* 2010, Goldstein *et al.* 2011, Fifth Joint Task Force of the European Society of Cardiology 2012, Goff *et al.* 2013, Bushnell *et al.* 2014, Kernan *et al.* 2014).

Established Risk Factors	**Other Factors Associating with an Elevated Risk of CVD Events**
Adverse dietary habits	Age
Cigarette smoking	Air pollution
Diabetes mellitus	Atrial fibrillation
Elevated total serum cholesterol	Changes in hormonal status (specific for women)
Hypertension	Chronic kidney disease
Obesity	Decreased serum high density lipoprotein cholesterol level
	Drug abuse
	Elevated serum homocysteine concentration
	Erectile dysfunction
	Family history of premature CVD events
	Gestational diabetes
	Glucose intolerance
	Heavy alcohol consumption
	History of pre-eclampsia
	Lack of fish consumption (n-3 fatty acids)
	Male gender
	Mental illness (depression, exhaustion, phobic anxiety)
	Migrane with aura
	Oral contraceptives
	Physical inactivity
	Prior cardiovascular disease
	Postmenopausal hormone use
	Pregnancy
	Prothrombotic factors (e.g. fibrinogen)
	Race
	Seasonal factors (temperature effects)
	Sickle Cell Disease
	Sleep apnea
	Social deprivation

In addition, infections, such as influenza, the presence of oral pathogens or underlying (auto) immune diseases like lupus erythematosus, Wegener's granulomatosis or rheumatoid arthritis are likely to play a role (Legein *et al.* 2013, Goldstein *et al.* 2011). Nonetheless, only 60% of the attributable risk for ischemic stroke can be explained by the identified risk factors whereas for CHD the corresponding proportion is 90% (Donnan *et al.* 2008). Furthermore, the importance of some CVD risk factors deviates between the two entities. Age is probably the strongest determinant for both CHD and ischemic stroke with a linear increase in the prevalence for ischemic stroke and with a peak in prevalence for CHD among those aged 50 to 70 years (Soler and Ruiz 2010). With respect to the major modifiable risk factors for CVD (Table 2.1) high blood pressure, smoking, dyslipidemia, diabetes and obesity all have similar relevance in CHD while high blood pressure, the most important risk factor for any form of stroke, and smoking account for the majority of the identified etiological factors for ischemic stroke (Soler and Ruiz 2010).

With respect to the major risk factors for CVD, the role of elevated total serum cholesterol, in the form of elevated serum LDL cholesterol, and diabetes lie within the scope of this thesis and will, therefore, be reviewed below.

2.1.3 Low density lipoprotein and cardiovascular disease

A strong correlation exists for average serum total cholesterol values and CHD event occurrence (Law and Wald 2002). The association between a high serum cholesterol level and the risk of CHD was already noted in the Framingham Study (Kannel *et al.* 1971). In 1984 the first confirmation of causality emerged when The Lipid Research Clinics Coronary Primary Prevention Trial detected a 20% risk reduction in CHD events among men treated with cholestyramine, in comparison to placebo (Anonymous 1984). However, it was not until the publication of the 4S in 1994 that a statistically significant and clinically relevant decrease in all-cause mortality was observed for any cholesterol-lowering agent (Steinberg 2006, Scandinavian Simvastatin Survival Study Group 1994). Subsequently, many clinical and observational studies have concentrated on the effects of lowering serum LDL cholesterol on the risk of CHD events (Marmot and Elliot 2005). Although an inverse association exists between high density lipoprotein (HDL) cholesterol levels and the risk of CHD events, the role of HDL cholesterol in the aetiology of CHD is thought to be less profound than that of LDL cholesterol (Marmot and Elliot 2005).

LDL cholesterol concentrations are determined by LDL production in the liver and the rate of LDL uptake via hepatic LDL receptors (Goldstein and Brown 1977). The diversity of activities underlying what eventually will present as an elevated LDL serum concentration allows for various pharmacological approaches such as niacin (nicotinic acid), bile acid sequestrants, fibrates, ezetimibe and statins (Backes *et al*. 2005). Although, all of these drugs have beneficial effects, statins reduce LDL cholesterol concentration to the greatest extent (Backes *et al*. 2005). The subsequent decrease in the risk of CVD events with statins, as noted in various patient subgroups, (Cholesterol Treatment Trialists' Collaboration 2010) exceeds those attained with the other pharmacological approaches (Preiss and Sattar 2009, Jun *et al.* 2010). The findings from large RCTs

also support the role of reducing LDL in CVD prevention rather than the other lipoproteins. In studies conducted by the AIM-HIGH Investigators (2011) and by the HPS2-THRIVE Collaborative Group (2014) niacin or placebo was administered as an add-on therapy for patients with atherosclerotic CVD and intensive statin therapy. Niacin improves the levels of all major lipoproteins and is the best available lipid-lowering drug (LLD) to significantly reduce the lipoprotein (a) and to increase HDL (Backes *et al.* 2005). Nonetheless, in both studies, niacin failed to confer any additional benefit to that achieved with statin therapy in CVD, despite the observed improvements in HDL (AIM-HIGH Investigators 2011, HPS2-THRIVE Collaborative Group 2014). Recently, a humanized monoclonal antibody targeted to block the interaction between the proprotein convertase subtilisin/kexin type 9 serine protease (PCSK9) and LDL receptor has been shown to reduce the LDL concentration by 40 to 60% in healthy subjects already receiving statin therapy (Stein *et al.* 2012). However, the long-term effects of PCSK9 inhibitors on cardiovascular outcomes remain to be determined as the first phase III clinical trials are currently recruiting patients (available at www. clinicaltrials.gov, accessed in May 2014). Nonetheless, the preliminary findings from the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (Cannon *et al.* 2008) that were presented at the American Heart Association´s Scientific Sessions 2014 Conference (Available at http://newsroom.heart.org, accessed in Jan 2015) suggested that add-on ezetimibe therapy reduces LDL cholesterol level and subsequent CVD events to a greater extent in comparison to statin monotherapy. This can be interpreted as to reaffirm the role of reducing LDL in CVD prevention.

2.1.4 Diabetes and cardiovascular disease

Diabetes is a chronic disease where either the pancreas does not produce enough insulin or the body cannot effectively use the insulin produced (Diabetes: Current Care Guidelines 2013). Traditionally diabetes has been classified into two clinical categories with a distinct aetiology: Type 1 diabetes, which is usually characterized by its total insulin deficiency whereas in type 2 diabetes there is typically both a progressive defect in insulin secretion and peripheral insulin resistance (Diabetes: Current Care Guidelines 2013, American Diabetes Association 2014). However, the variety of aetiologies extends even beyond that and there now exists a consensus that there are several subtypes of diabetes. It is also recognized that the classification is somewhat artificial i.e. not all patients can be clearly classified as type 1 or type 2 diabetic (Diabetes: Current Care Guidelines 2013, American Diabetes Association 2014). The current Finnish clinical guideline also considers diabetes to manifest itself as a continuum of the different subtypes and, therefore, does not make a clear distinction between them. Instead, physicians are recommended to focus on the clinical severity of the disease and the overall prevention of complications (Diabetes: Current Care Guidelines 2013). However, over 75% of Finnish patients with diabetes are considered to have type 2 diabetes, and the literature review in this thesis, therefore, will focus on this form of diabetes.

The prevalence of diabetes depends on the applied diagnostic criteria. In 2008, the global prevalence of diabetes was estimated to present in one out of every ten individuals aged

25 years and more (WHO 2011b). The WHO widened the criteria for type 2 diabetes in 1999 when the diagnostic threshold for fasting plasma glucose was lowered from 7.8 mmol/L to the current 7.0 mmol/L (for blood glucose from 6.7 mmol/L to 6.1 mmol/L) (WHO 1999) to be in line with the recommendation issued by the American Diabetes Association in 1997.

The diagnostic criteria for diabetes were reviewed, updated and re-published by the WHO in 2006. Correspondingly, the criterion for diabetes mellitus remained as fasting plasma glucose 7.0 mmol/L or more with alternative criteria introduced for a two-hour plasma glucose of 11.1 mmol/L or more following an oral glucose load (WHO 2006). The first Finnish Current Care Guideline with diagnostic criteria for diabetes was published in 2007 (Diabetes: Current Care Guidelines 2007). The diagnosis of diabetes was recommended to be based on diabetes-related symptoms (i.e. polydipsia, polyuria, weight loss) associated with an incidental plasma glucose value of 11 mmol/L or more. In the absence of diabetes-related symptoms, laboratory measurements obtained on at least two separate occasions with fasting plasma glucose value of 7mmol/L or more or, alternatively, a two-hour plasma glucose value of 11.0 mmol/L or more were considered as being diagnostic for diabetes. In addition to the above criteria, the current Finnish guideline on diabetes also includes a glycated haemoglobin (HbA1c) value of 48mmol/mol or more (equivalent to ≥ 6.5%) within it´s diagnostic criteria for diabetes (Diabetes: Current Care Guidelines 2013), in line with the current recommendations provided by the American Diabetes Association (Standards of Medical Care in Diabetes 2014).

The Finnish criteria for special reimbursement due to medication costs in diabetes, as provided by the Social Insurance Institution (SII), are used to define study populations in this thesis and are, therefore, described in table 2.2 with a glossary and description of the Finnish Reimbursement framework given in the Appendix. It is noteworthy that the diagnostic criteria for diabetes in the clinical treatment guidelines described above are wider than the eligibility criteria for special reimbursement in diabetes in Finland. As examples, by the end of years 2005, 2007 and 2008, 170 800, 184 500 and 198 000 Finnish individuals were eligible for special reimbursement for medication costs due to diabetes, correspondigly, accounting for 82%, 76% and 74% of all individuals with reimbursed purchases for antidiabetic pharmacotherapy classified with the Anatomical Therapeutic Chemical (ATC) code A10 (WHO 2013) during the respective years (National Agency for Medicines and The Social Insurance Institution 2006 -2009). In 2005 (a study year included in studies II-IV, see Methods, Table 4.2), 90% of the patients who received a new entitlement for special reimbursement due to diabetes were considered as having type 2 diabetes.

Diabetes of any type demands continuing medical care and patient self-management to prevent the acute and long-term complications (American Diabetes Association 2014, Diabetes: Current Care Guidelines 2013). Overall, the pathology of atherosclerosis among patients with diabetes is very similar to that of their non-diabetic peers, but insulin resistance and hyperglycaemia substantially increase the risk of CVD and heart failure, and the relative risk for CHD is especially high in type 1 diabetes (Laakso and

Kuusisto 2014). The CVD morbidity in type 2 diabetes is characterized by the higher incidence of macrovascular complications (including CHD, cerebrovascular events and PAD) compared to that of microvascular events (e.g. retinopathy, nephropathy and neuropathy) (Turner *et al.* 1996).

The main aim of antidiabetic treatment is to prevent microvascular events with less significant effect in preventing macrovascular events (ADVANCE Collaborative Group 2008). Traditionally, persons with diabetes have been considered to have at least twice the risk of suffering an ischemic stroke and coronary heart disease as compared to their nondiabetic peers (Haffner *et al.* 1998, Schramm *et al.* 2008, Emerging Risk Factors Collaboration 2010, Matikainen *et al.* 2010). However, it seems that currently not all patients with diabetes carry as high a CVD risk (Kuusisto and Laakso 2013).

Table 2.2. Criteria as provided by the SII, Finland, for the special reimbursement in diabetes (code 103) in 1995 to 2014 with a special emphasis on the relevant changes taking place since 1995 (Based on Pharmaca Fennica 2008-2013 and www.kela.fi).

Year	Criteria and relevant changes
1995	Diagnosis for type 1 diabetes mellitus: Ensured by a specialist or by competent hospital staff. Diagnosis for type 2 diabetes mellitus: 1) diabetes-related symptoms (i.e. polydipsia, polyuria, glucosuria) together with fasting blood glucose ≥ 7mmol/L or 2) in the absence of diabetes-related symptoms several laboratory measurements with fasting blood glucose ≥ 7mmol/L. In all cases of type 2 diabetes, the antidiabetic pharmacotherapy was to last for 6 months prior to application for special reimbursement. In obesity, the eligibility criteria also included a 6-month dietary intervention prior to antidiabetic pharmacotherapy. The information on clinically relevant outcomes of both aforementioned interventions was to be included in the application. Gestational diabetes requiring insulin therapy in a previously healthy woman did not allow for special reimbursement unless the need for insulin therapy was prolonged.
2006	Diagnosis for type 2 diabetes mellitus: Alternatively a fasting plasma glucose ≥8mmol/L.
2008	Diagnosis for type 2 diabetes mellitus: Fasting blood glucose ≥ 6.1 mmol/L (or fasting plasma glucose ≥ 7.0 mmol/L) or an incidental plasma glucose ≥11.1mmol/L (≥10mmol/L for blood glucose). The criteria for obesity were defined as a body mass index (BMI) of ≥25kg/m2. The 6-month dietary intervention was no longer required prior to the initiation of antidiabetic pharmacotherapy for patients with severe hyperglycaemia.
2012	Diagnosis for type 2 diabetes mellitus: The 6-month dietary intervention required prior to the initiation of antidiabetic pharmacotherapy was omitted for all subjects.
2014	Diagnosis for type 2 diabetes mellitus: An alternative two-hour plasma glucose ≥ 11.1 mmol/L (≥10.0 mmol/L for blood glucose) following an oral glucose load or an HbA1c value of ≥ 48mmol/mol equivalent to ≥ 6.5%.

The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated an association between increased concentrations of LDL cholesterol, decreased concentrations of HDL cholesterol, raised systolic blood pressure, hyperglycaemia, and smoking and the incidence of CHD events in diabetes (Turner *et al.* 1998). Additionally, the duration of diabetes and female gender further increase the risk of CHD in diabetes independently of coexisting, other risk factors (Fox *et al*. 2004, Emerging Risk Factors Collaboration 2010, Kuusisto and Laakso 2013). Concordantly, the medical treatment in diabetes is complex. In addition to treating high plasma glucose levels it aims to prevent CVD events by simultaneously covering all major CVD risk factors including the management of dyslipidemia with statins (Table 2.3).

The dyslipidemia in type 2 diabetes is characterized by a high serum triglyceride concentration, low HDL cholesterol concentration, and small dense LDL particles, which increase the risk of CVD events (Taskinen 2005). Furthermore, diabetic individuals have been considered to have a doubled risk for CVD events in comparison to their nondiabetic peers, similar to those without diabetes but with established CVD (Haffner *et al*. 1998, Schramm *et al*. 2008, Matikainen *et al.* 2010). The current European and American guidelines for dyslipidaemia and CVD prevention recommend statin therapy for nearly all patients with type 2 diabetes mellitus, also for those without CVD (The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology and the European Atherosclerosis Society 2011, Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice 2012, National Institute for Health and Care Excellence 2010, American Diabetes Association 2014). Only patients under the age of 40 years, with newly diagnosed type 2 diabetes, and without clinical complications or other CVD risk factors, may not be deemed candidates for statin therapy (The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology and the European Atherosclerosis Society 2011). The recommendations are based on the evidence derived from meta-analyses of statin RCTs showing consistent treatment effects in subgroups of patients with diabetes (Brugts *et al.* 2009, Cholesterol Treatment Trialists' Collaboration 2010), or on the individual RCTs either consisting of only patients with diabetes or reporting subanalyses on diabetes (Pyörälä *et al.* 1997, Goldberg *et al.* 1998, Collins *et al.* 2003, Colhoun *et al.* 2004, LaRosa *et al.* 2005, Sever *et al*. 2005, Knopp *et al.* 2006).

Table 2.3. Pharmacological treatment of diabetes mellitus according to guidelines on diabetes care (American Diabetes Association 2014, Diabetes: Current Care Guidelines 2013, National Institute for Health and Care Excellence 2010) and categorized according to the 5th level of the ATC classification of drugs valid in Aug 2014 (WHO 2013).

Antihypertensive agents	**Blood glucose lowering agents**	**Lipid lowering agents**	**Antithrombotic agents**
ACE-inhibitors	Insulins and its analogues	Statins	Platelet aggregation inhibitors
Angiotensin II antagonists	Biguanides (Metformin)	Fibrates	
Diuretics	Sulphonylureas	Bile acid sequestrants	
Calcium channel blockers	Thiazolidinediones	Ezetimibe	
Beta-adrenergic antagonists	Dipeptidyl peptidase 4 (DPP-4) inhibitors		
	Other blood glucose lowering agents		

2.2 Statins

2.2.1 Clinical pharmacology of statins

2.2.1.1 Mechanism of action

Statins act by competitively inhibiting the hydroxymethylglutarylcoenzyme A (HMG-CoA) reductase. This prevents the HMG-CoA reductase from catalysing the conversion of HMG-CoA to mevalonate, which is the rate-limiting step in cholesterol synthesis (Schacter 2005). As a result, hepatocyte cholesterol synthesis declines and the liver's ability to remove the LDL already in the blood increases due to an up-regulation of the hepatic LDL receptors (Backes *et al.* 2005, Schacter 2005). Then the serum LDL concentration decreases in a dose and statin type dependent manner (Law *et al.* 2003). For example, atorvastatin 10mg is considered to reduce LDL cholesterol by 38%, similarly to simvastatin 20mg (www.fda.gov, accessed in April 2012, Weng *et al.* 2010, Dyslipidemia: Current Care Guidelines 2013). A reduction in LDL of more than 40% seems achievable with rosuvastatin at a daily dose of 5mg, with atorvastatin 20 mg or with simvastatin 40mg but a reduction of more than 60% seems achievable only with high dose rosuvastatin (40mg) (www.fda.gov, Weng *et al.* 2010). Additionally, statins increase HDL and decrease triglyceride concentrations although to a lesser extent (Weng *et al.* 2010).

In CVD statins are also claimed to have antithrombotic, anti-inflammatory, endothelial, angiogenesis promoting and plaque stabilizing effects not mediated through the reduction in LDL levels (Mihos *et al.* 2010). These additional effects are sometimes referred to as "pleiotropic" (Mihos *et al.* 2010, Sirtori 2014). Statins improve endothelial function and reduce the size and the vulnerability of the atheromatous plaque (Crisby *et al.* 2001, Sirtori 2014) in a dose and statin type dependent manner (Nissen *et al.* 2004). However, when compared to the evidence supporting the LDL reducing mechanism of action in preventing major CVD events (Baigent *et al.* 2005), the evidence for these supplemental beneficial statin effects is inconclusive (Robinson *et al.* 2005).

2.2.1.2 Types of statins

The first statin, lovastatin, was granted market authorization in 1987. Currently, there are six statins available on the Finnish drug market: simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin and rosuvastatin. Of these, lovastatin, pravastatin and simvastatin are fungal derived agents and atorvastatin, fluvastatin and rosuvastatin are fully synthetic compounds (Schachter 2005). Cerivastatin was withdrawn from the global drug market in 2001 due to deaths attributed to rhabdomyolysis and subsequent kidney failure (Furberg and Pitt 2001). Rhabdomyolysis was found to be 10 times more common with cerivastatin than with the other statins and was higher among patients who received the maximal dose and those who received gemfibrozil concomitantly. Gemfibrozil inhibits the hepatic cytochrome P450 metabolism of cerivastatin, which leads to elevated cerivastatin plasma concentrations and, therefore, an increased risk for myotoxicity (Neuvonen *et al.* 2006). It is now recognized that statins undergoing hepatic metabolism via the cytochrome P450

pathway (simvastatin, lovastatin, fluvastatin and atorvastatin) are more susceptible for drug-drug interactions and adverse drug reactions as compared to statins that are excreted mainly unchanged (pravastatin and rosuvastatin) (Schachter 2005, Neuvonen *et al.* 2006).

2.2.1.3 Efficacy

Extensive double-blind RCTs have demonstrated that statins are effective in reducing CVD events in patients with or without pre-existing CVD. At the meta-analysis level, statins reduce the relative risk for all-cause mortality by 12%, coronary mortality by 19%, myocardial infarction or coronary death by 23%, the need for coronary revascularisation by 24% and fatal or non-fatal stroke by 17% for every 1 mmol/L reduction in LDL cholesterol, in comparison to placebo (Baigent *et al.* 2005). The protective effect for major CVD events becomes apparent already after the first year from randomisation, subsequently increases and lasts after 5 years of follow-up (Baigent *et al.* 2005). There are indications from the post-trial periods that the legacy effect of in-trial statin use could, in fact, last up to five extra years (Strandberg *et al.* 2004, Heart Protection Study Collaborative Group 2011, Packard *et al.* 2014). An additional 15% relative reduction is achieved in the incidence of major vascular events (fatal or non-fatal CHD and ischemic stroke) with more intensive regimens (i.e. simvastatin 80mg, atorvastatin 40-80mg) being associated with an additional reduction in LDL levels of 0.5mmol/L (mean), as compared to less intensive regimens (i.e. pravastatin 40mg, simvastatin 20-40mg) (Cholesterol Treatment Trialists' Collaboration 2010).

The size of the absolute treatment effect achieved with statins correlates with the patient´s background risk for CVD events and the absolute reduction in LDL gained with statin therapy (Baigent *et al.* 2005). Table 2.4 describes the basic features of the large, landmark double-blind statin RCTs revealing the primary efficacy in CVD prevention and survival as identified from clinical treatment guidelines (Dyslipidemia: Current Care Guidelines 2013, Task Force for the Management of Dyslipidaemias of the European Society of Cardiology and the European Atherosclerosis Society 2011) and meta-analyses (Cholesterol Treatment Trialists' Collaboration 2010, Cholesterol Treatment Trialists' Collaboration 2012, Brugts *et al.* 2009, Cannon *et al.* 2006). It is noteworthy that the majority of patients included in the earliest RCTs already suffered from established CHD (Scandinavian Simvastatin Survival Study Group 1994, Sacks *et al.* 1996, The LIPID Study Group 1998) and were men aged up to 75 years. In 2002, with the publication of the Heart Protection Study (HPS), the Lescol Intervention Prevention Study (LIPS) and the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) (Heart Protection Study Collaborative Group 2002, Serruys *et al.* 2002, Shepherd *et al.* 2002) the knowledge on the benefits of statins extended beyond the age of 75 years.

While the proportions of trial participants presenting with diabetes mellitus are presented for all the individual studies included in Table 2.4, Table 2.5 further describes the available trial evidence for statin treatment in diabetes as identified from clinical treatment guidelines on diabetes (American Diabetes Association; Standards of Medical Care in Diabetes 2014, Diabetes: Current Care Guidelines 2013).

Table 2.4. Description of the landmark double-blind randomised controlled statin trials.

Study (year of publication)	Patients (N)	Treatments (mg per day)	Median follow-up (y)	Women (%)	Mean/median age (y), (min, max)	Prior CVD (%)	DM (%)	Relative Risk of major CVD events or mortality (95% CI)*
More vs. less statin								
PROVE-IT (2004)	4162	A80 vs. P40	2,0	22	58 (min 18)	100	18	CVD: 0.84 (0.74–0.95)
TNT (2005)	10001	A80 vs. A10	5,0	19	61(35,75)	100	15	CVD: 0.78 (0.69–0.89)
Statin vs. control								
4S (1994)	4444	S20-40 vs. PO	5,4	19	59[1](35,70)	100	5	Mortality:0.70 (0.58–0.85)
WOSCOPS (1995)	6595	P40 vs. PO	4,9	0	55 (45,64)	NA	1	CVD: 0.69 (0.57–0.83)
CARE (1996)	4159	P40 vs. PO	5,0	14	59 (21,75)	100	14	CVD: 0.76 (0.64–0.91)
AFCAPS/TexCAPS (1998)	6605	L20-40 vs. PO	5,2	15	58 (45/55,73)	0	4	CVD: 0.63 (0.50–0.79)
LIPID (1998)	9014	P40 vs. PO	6,1	17	62 (31,75)	100	9	CVD mortality: 0.76 (0.65–0.88)
LIPS (2002)	1677	F80 vs. PO	3,9	16	60 (18,80)	100	12	CVD: 0.78 (0.64–0.95)
HPS (2002)	20536	S40 vs. PO	5,4	25	NA (40,80)	NA	29	Mortality: 0.87 (0.81–0.94)
PROSPER (2002)	5804	P40 vs. PO	3,2	52	75 (70-82)	44	11	CVD: 0.85 (0.74–0.97)

ASCOT-LLA (2003)	10305	A10 vs. PO	3,3	19	63 (40,79)	NA	25	CVD: 0.64 (0.50–0.83)
CARDS (2004)	2838	A10 vs. PO	3,9	32	62 (40,75)	0	100	0.63 (0.48–0.91)
SPARCL (2006)	4731	A80 vs. PO	4,9	41	63 (min 18)	100	17	CVD (stroke): 0.84 (0.71–0.99)
JUPITER (2008)	17802	R20 vs. PO	1,9	38	66 (min 50/60)	0	<1	CVD: 0.56 (0.46–0.69)
SHARP (2011)	9270	S20+EZ10 vs. PO	4,9	37	62 (min 40)	15	23	CVD: 0.83 (CI 0.74–0.94)

[1]For the statin treated group. *As provided for the primary study outcome. Note: Studies used somewhat different primary outcomes for CVD events. Abbreviations of the trials: AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study (Downs *et al.* 1998); ASCOT-LLA=Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (Sever *et al.* 2003); CARDS=Collaborative Atorvastatin Diabetes Study (Colhoun *et al.* 2004); CARE=Cholesterol And Recurrent Events (Sacks *et al.* 1996); HPS=Heart Protection Study (Heart Protection Study Collaborative Group 2002); JUPITER=Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin study group (Ridker *et al.* 2008); LIPID=Long–term Intervention with Pravastatin in Ischaemic Disease (The LIPID Study Group1998).; LIPS=Lescol Intervention Prevention Study (Serreus *et al.* 2002); PROSPER=Prospective Study of Pravastatin in the Elderly at Risk (Shepherd *et al.* 2002); PROVE-IT=Pravastatin or Atorvastatin Evaluation and Infection Therapy study (Ray *et al.* 2005); SHARP=Study of Heart and Renal Protection (SHARP Collaborative Group 2010); SPARCL= Stroke Prevention by Aggressive Reduction in Cholesterol Levels (Amarenco *et al.* 2006); 4S=Scandinavian Simvastatin Survival Study (Scandinavian Simvastatin Survival Study Group 1994); TNT=Treating to New Targets study (LaRosa *et al.* 2005); WOSCOPS=West of Scotland Coronary Prevention Study (Shepherd *et al.* 1995). Other abbreviations: A=Atorvastatin; CI=Confidence Interval; CVD=Cardiovascular disease; DM= Diabetes mellitus; EZ=Ezetimibe; F=Fluvastatin; L=Lovastatin; NA= Not available; P=Pravastatin; PO=Placebo; R=Rosuvastatin; S=Simvastatin.

Table 2.5. Description of double-blind randomised controlled statin trials in subjects with diabetes.

Study (year of publication)	Number of patients	Treatment comparison (mg per day)	Median follow-up (y)	Women (%)	Mean/median age (y), (min, max)	Prior CVD (%)	Prior MI (%)	Relative Risk of major CVD events or mortality (95% CI)[1]
Trials where all participants were subjects with diabetes								
CARDS (2004)	2838	A10 vs. PO	3,9	32	62 (40,75)	0	0	CVD: 0.63 (0.48-0.91)
ASPEN (2006)	2410	A10 vs. PO	4,0	34	61 (40,75)	NA	16	CVD: 0.90 (0.73-1.12)
Subanalyses of subjects with diabetes								
4S (1997)	202	S20-40 vs.PO	5,4	22	60 (35,70)	100	63	Mortality: 0.57 (0.30-1.08)
CARE (1998)	586	P40 vs. PO	5,0	20	61 (21,75)	100	100	CVD: 0.87 (NA, NS)
HPS (2003)	5963	S40 vs. PO	5,4	30	62 (40,80)	51	19	CVD: 0.78 (0.70-0.87)
ASCOT-LLA (2005)	2532	A10 vs. PO	3,3	24	64 (40,79)	12	0	CVD: 0.84 (0.55-1.29)
TNT (2006)	1501	A80 vs. A10	5,0	27	63 (35,75)	100	57	CVD: 0.75 (0.58-0.97)

[1]Studies used somewhat different primary outcomes. Abbreviations of the trials (first author): ASCOT-LLA=Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (Sever *et al.* 2005); ASPEN= The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (Knopp *et al* 2006); CARDS=Collaborative Atorvastatin Diabetes Study (Colhoun *et al.* 2004); CARE=Cholesterol And Recurrent Events (Goldberg *et al.* 1998); HPS=Heart Protection Study (Collins *et al.* 2003); 4S=Scandinavian Simvastatin Survival Study (Pyörälä *et al.* 1997); TNT=Treating to New Targets study (LaRosa *et al.* 2005). Other abbreviations: A=Atorvastatin; CI=Confidence Interval; CVD=Cardiovascular disease; F=Fluvastatin; NA= Not available; NS= Not statistically significant; P=Pravastatin; PO=Placebo; S=Simvastatin.

Additionally, a large meta-analysis of 14 RCTs and including only participants with diabetes detected a relative reduction of 21% for major vascular events (i.e. coronary event, coronary revascularisation or stroke) for every 1mmol/L reduction in LDL cholesterol associated with statin therapy (Cholesterol Treatment Trialists' Collaborators 2008) and confirmed the efficacy of statins in diabetes as had been suggested by the individual RCTs.

2.2.1.4 Safety

The early toxicology studies indicated that statins might be hepatotoxic (Chalasani 2005). The presence of hepatic dysfunction has also been considered as a risk factor for statin-induced adverse effects (Schachter 2005). This derives from the fact that the metabolism for the majority of statins takes place primarily in the liver (Knopp 1999). Hence, several statin RCTs have excluded patients with either chronic liver disease or abnormal liver function tests prior to randomisation (Scandinavian Simvastatin Survival Study Group 1994, Heart Protection Study Collaborative Group 2002, The LIPID Study Group 1998, LaRosa *et al.* 2005, Ray *et al.* 2005, Ridker *et al*. 2008). Active liver disease or elevated transaminase values (three times the upper level of normal) have also been described as contraindications for therapy with all statins, including even those with marginal hepatic metabolism (product information for Crestor®, Lescol®, Lipitor®, Lovastatin ratiopharm®, Pravastatin Orion® and Zocor®, valid in April 2014). Furthermore, a recent meta-analysis on observational statin studies identified an increased risk of raised liver enzymes associating with statin use (Macedo *et al.* 2014) However, the early statin trials did not report on findings of excess hepatotoxicity among the statin treated groups when compared to placebo (Scandinavian Simvastatin Survival Study Group 1994, Sacks *et al*. 1996, Shepherd *et al.* 1995, The LIPID Study Group 1998) and nowadays statins are not considered as hepatotoxic (Dyslipidemia. Current Care Guidelines 2013). In fact, the beneficial effects of statins in non-alcoholic fatty liver disease and non-alcoholic steatohepatitis are under current investigation (Eslami *et al.* 2013).

Statin use is associated with various muscle complaints (product information for Crestor®, Lescol®, Lipitor®, Lovastatin ratiopharm®, Pravastatin Orion® and Zocor®, valid in April 2014) and based on observational data, with a two to three fold increased risk of myopathy (Macedo *et al.* 2014). However, the case numbers retrieved from 30 statin RCTs showed that the incidence of clinically meaningful myositis, when defined as muscle pain with an increase in the serum creatinine kinase (CK) greater than ten times the upper level of normal, is, in fact,0.1% both among the statin and placebo treated groups (based on Thompson *et al.* 2003). The incidence of rhabdomyolysis, defined as markedly elevated CK levels together with nephropathy, was a tenth of that for myositis, with no significant differences between the statin and placebo treated groups (Thompson *et al.* 2003). This is in line with the incidence of rhabdomyolysis reported in a meta-analysis of RCTs for low dose statin regimens (5 year excess: 0.01%, Standard error 0.01) (Baigent *et al.* 2005) and indicates that clinically meaningful adverse muscle reactions induced by statins are very rare. However, there is great intersubject variability in the predisposition for statin induced myopathy that is influenced by genetic factors. A statin trial involving 12 000 subjects yielded 85 subjects with definite or incipient myopathy, all

occurring after taking simvastatin 80mg daily (SEARCH Collaborative Group 2008). In further genome wide analyses, a strong association was found between the risk of statin induced myopathy and a single-nucleotide polymorphism (T>C) located within the SLCO1B1 gene on chromosome 12. SLCO1B1 encodes the organic anion transporting polypeptide 1B1 (OATP1B1) which is involved in the hepatic uptake of statins (Niemi *et al.* 2011). The T>C variant is associated with a decreased transport activity of the OATP1B1 (Niemi *et al.* 2011). Furthermore, a markedly increased exposure especially to simvastatin acid, the active metabolite of simvastatin, has been demonstrated in those subjects who are of homozygous SLCO1B1 CC genotype as compared with those with the TC and TT genotypes (Pasanen *et al.* 2006, Niemi *et al.* 2011).

During the early development stages of statins there was considerable concern over their carcinogenic properties (Steinberg 2006). However, the cumulative exposure data from 22 randomised controlled statin trials and over 130 000 subjects with an average of 5 years of follow-up did not detect any risk for this kind of adverse effect (Cholesterol Treatment Trialists' Collaboration 2012). However, high dose atorvastatin (80mg) did increase the relative risk for hemorrhagic stroke in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial among patients with a recent stroke or transient ischemic attack (Amarenco *et al.* 2006). Nonetheless, the 16% reduction in the primary composite end point of nonfatal or fatal stroke was statistically significant among the atorvastatin treated group in the trial and this was driven by the reduction in the ischemic stroke events (Hazard ratios, HRs, 0.78 for ischemic stroke and 1.66 for haemorrhagic stroke) (Amarenco *et al.* 2006). At the meta-analysis level, no sign of an increased risk for haemorrhagic stroke with statins has been identified while the efficacy in reducing all stroke events has been confirmed (Amarenco and Labreuche 2009). Combined data from 21 statin RCTs also helped to refute the association between statin exposure and the increased risk of acute pancreatitis (Preiss *et al.* 2012) as had been previously suggested in some observational studies (Singh and Loke 2006, Tsigrelis and Pitchumoni 2006). Nonetheless, a recent meta-analysis of 13 statin trials indicated that statins increase the relative risk of new-onset type 2 diabetes by 9% in comparison to control treatments (Sattar *et al*. 2010). This corresponds to one additional case of diabetes per 255 patients treated with statins for 4 years (Sattar *et al.* 2010) and the risk proved to be dose-dependent (Preiss *et al.* 2011).

Taken together, a recent systematic review on 14 primary prevention statin trials and 15 secondary prevention trials observed no statistically significant increase in the rate of serious adverse events (defined as medical occurrences that either resulted in death, were life threatening, required hospitalization, or resulted in an intervention) for those treated with statins when compared to placebo (Finegold *et al*. 2014). Similarly, there were no statistically significant differences in the rates of rhabdomyolysis, symptomatic raised serum CK levels, back pain, muscle aches, headache, newly diagnosed cancer, gastrointestinal disturbances, renal disorder or myopathy associated with symptomatically raised CK between the statin and placebo treated groups. The statistically significant adverse events recorded were elevated liver enzymes (>3 times the upper level of normal) and newly diagnosed diabetes with absolute risks of 0.4% and 0.5%, respectively, during an average follow-up of 2 to 5 years. One in every five (20%) of all new diabetes cases

diagnosed during statin therapy were attributable to statins. Withdrawals were reported in 12-13% of patients receiving statins and 13-15% of patients receiving placebo (Finegold *et al*. 2014). However, the eligible trials in the review were predominantly conducted with low-strength statin regimens, and given the dose dependent nature of adverse drug reactions, this may have underestimated the frequencies among the statin treated patients.

2.2.1.5 Clinical treatment guidelines for dyslipidemia

According to the current clinical guidelines, the main aim of initiating statin therapy in clinical practice is to lower the risk of CVD events, including CHD, stroke and PAD (Dyslipidemia: Current Care Guidelines 2013, The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology and the European Atherosclerosis Society 2011). This approach is based on the available clinical trial data on statin efficacy (Table 2.4).

The first Finnish Current Care Guidelines on the management of dyslipidemia were introduced in 2004 (Dyslipidemia: Current Care Guidelines 2004). The previous clinical guideline on dyslipidemia dated from 1993 and recommended that all pharmacological treatment for dyslipidemia, including statin therapy, should be initiated for all patients only after a reasonable dietary intervention had taken place (Suomen Sisätautilääkärien Yhdistys *et al.*1993). The first priorities for the dietary intervention presented in 1993 were patients with established CHD or another CVD and with an elevated cholesterol value of 8 mmol/L or more and patients presenting with hypertension or diabetes. In general, the Dyslipidemia Current Care Guideline introduced in 2004 were in line with the contemporary European guideline on dyslipidemia (De Backer *et al.* 2003). Although the European guidelines more strongly prioritised interventions to those with established CVD, both highlighted prompt interventions to those who after an individualised risk assessment were considered to be at a high risk for any future CVD event (De Backer *et al.* 2003, Dyslipidemia: Current Care Guidelines 2004). These included individuals with any established atherosclerotic CVD, with type 2 diabetes or with type 1 diabetes associated with microalbuminuria and also asymptomatic individuals with at least a 5% risk of fatal CVD event within 10 years (Dyslipidemia: Current Care Guidelines 2004). For these individuals, the target was an LDL value of less than 2.5mmol/L, and when necessary, pursued with pharmacological therapy, preferably consisting of a statin. Additionally, the evidence base for statin therapy was extended to women and the elderly. The guideline was updated in 2009 with futher emphasis given on the need for pharmacological therapy among those with established CVD. The target LDL value for patients with very high risk for future CVD events, i.e. patients with both CVD and diabetes, was lowered to 1.8mmol/L (Dyslipidemia: Current Care Guidelines 2009). A similar update followed in the European treatment guideline published in 2011 when an alternative treatment target of ≥ 50% reduction in LDL level was also introduced (The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology and the European Atherosclerosis Society 2011). In 2013, the Finnish Current Care Guidelines were further updated to include the same alternative treatment target (Dyslipidemia: Current Care Guidelines 2013).

The corresponding Finnish Current Care Guidelines on Diabetes were first introduced in 2007 and covered also treatment strategies for dyslipidemia (Diabetes: Current Care Guidelines 2007). The contents of the guideline concerning the treatment of diabetic dyslipidemia and the subsequent, relevant amendments are presented in Table 2.6 in parallel with the Finnish Current Care Guidelines and the European guidelines on the management of dyslipidemia. Taken together, Table 2.6 describes the shift of overall dyslipidemia treatment away from the prevention of CHD alone to that also covering the prevention of other major CVD events in parallel with the decrease in the LDL level treatment targets and the increase in the proportion of the general population meeting the criteria to be classified as first priority patients. Simultaneously, Table 2.6 describes the efficiency of the dyslipidemia management in diabetes already introduced in 2007 (Diabetes: Current Care Guidelines 2007).

Table 2.6. Changes in three relevant guidelines on the treatment of dyslipidemia between the years 1993 and 2013.

Year	European guidelines (Wood D *et al.* 1998, De Backer *et al.* 2003, Graham *et al.* 2007, European Association for Cardiovascular Prevention & Rehabilitation 2011)	Suomen Sisätautilääkärien Yhdistys *et al.* 1993, Dyslipidemia: Current Care Guidelines 2004, 2009, 2013.	Diabetes: Current Care Guidelines 2007, 2009, 2011, 2013.
1993	Not applicable.	Aim of therapy: Prevention of CHD. Therapy: lifestyle intervention preceding pharmacological treatment with statins, fibrates, bile acid sequestrants or guargum. LDL treatment target for all: <3.5mmol/L. First priority: patients with established CHD or other atherosclerotic CVD, with highly elevated total cholesterol level ≥8.0 mmol/L, with hypertension or diabetes.	Not applicable
1994	Aim of therapy: Prevention of CHD. Therapy: lifestyle intervention preceding pharmacological treatment with statins, fibrates, bile acid sequestrants, guargum or nicotinic acid. LDL treatment target: Not available. Total cholesterol < 6.0 mmol/L. First priority: patients with established CHD or other atherosclerotic CVD.	Not applicable.	Not applicable.

Table 2.6. Changes in three relevant guidelines on the treatment of dyslipidemia between the years 1993 and 2013. *(Continued).*

Year	European guidelines (Wood D *et al.* 1998, De Backer *et al.* 2003, Graham *et al.* 2007, European Association for Cardiovascular Prevention & Rehabilitation 2011)	Suomen Sisätautilääkärien Yhdistys *et al.* 1993, Dyslipidemia: Current Care Guidelines 2004, 2009, 2013.	Diabetes: Current Care Guidelines 2007, 2009, 2011, 2013.
1998	Aim of therapy: Prevention of CHD (CVD). Therapy: lifestyle intervention preceding pharmacological treatment primarily with statins. LDL treatment target: <3.0mmol/L. First priority populations: patients with established CHD or other atherosclerotic CVD or asymptomatic patients with a ≥ 20% risk for CHD within 10 years.	Not applicable.	Not applicable.
2003	Aim of therapy: Prevention of CVD. LDL treatment target: in CVD or diabetes <2.5mmol/L. First priority: patients with established atherosclerotic CVD.	Not applicable.	Not applicable.
2004	Not applicable.	Aim of therapy: Prevention of CVD. Therapy: lifestyle intervention preceding pharmacological treatment primarily with statins. LDL treatment target: <3.0 mmol/L but in CVD or diabetes (or other high risk of CVD) <2.5mmol/L. First priority: patients with established atherosclerotic CVD, type 2 diabetes or type 1 diabetes with microalbuminuria or patients with ≥ 5% risk of a fatal CVD event within 10 years.	Not applicable.

2007	Therapy: lifestyle intervention already in combination with pharmacological therapy primarily with statins considerable for high risk patients. LDL treatment target in CVD or diabetes even <2.0mmol/L.	Not applicable	Aim of therapy: Prevention of CVD. Therapy: lifestyle intervention preceding pharmacological treatment primarily with statins for all, in CVD statin therapy without preceding lifestyle intervention. LDL treatment target: <2.5mmol/L, in CVD <.1.8mmol/L.
2009	Not applicable.	Immediate initiation of high dose statin therapy in case of an acute CHD event. LDL treatment target: <1.8 mmol/L in very high risk of CVD events.	No relevant amendments.
2011	LDL treatment target: <1.8 mmol/L in very high risk of CVD events or alternatively, 50 % reduction in LDL level. First priority: patients with established atherosclerotic CVD, type 2 diabetes or type 1 diabetes with microalbuminuria, high levels of individual risk factors, moderate to severe chronic kidney disease and asymptomatic patients with ≥ 5% risk a of fatal CVD event within 10 years.	Not applicable	No relevant amendments.

Table 2.6. Changes in three relevant guidelines on the treatment of dyslipidemia between the years 1993 and 2013. *(Continued).*

Year	European guidelines (Wood D *et al.* 1998, De Backer *et al.* 2003, Graham *et al.* 2007, European Association for Cardiovascular Prevention & Rehabilitation 2011)	Suomen Sisätautilääkärien Yhdistys *et al.* 1993, Dyslipidemia: Current Care Guidelines 2004, 2009, 2013.	Diabetes: Current Care Guidelines 2007, 2009, 2011, 2013.
2013	Not applicable	Therapy: lifestyle intervention in combination with pharmacological therapy (statins). LDL treatment target: <1.8 mmol/L in very high risk of CVD events or alternatively, 50 % reduction in LDL level. First priority: patients with established atherosclerotic CVD, diabetes of any type, high levels of individual risk factors, one severe risk factor, moderate to severe chronic kidney disease, hereditary dyslipidemia or LDL ≥6.0mmol/L, or patients with ≥ 5% risk of a fatal CVD event within 10 years.	LDL treatment target: <2.5mmol/L, in CVD <.1.8mmol/L, or alternatively, 50 %:reduction in LDL level.

Abbreviations: CHD= coronary heart disease; CVD= cardiovascular disease; LDL= low density lipoprotein.

2.2.2 Strengths and limitations of randomised, controlled statin trials

In general, the guideline developers as well as drug regulatory authorities and the pharmaceutical industry consider the randomised, double blinded, controlled clinical trials to be the "golden standard" with which to establish efficacy and safety of treatments (ICH harmonized tripartite guideline 1997, Guyatt 2008, Finnish Medical Society Duodecim 2012). This derives from the rigorously controlled, randomised study settings which have been designed to produce internally valid, unbiased evidence on drug effects (ICH harmonized tripartite guideline, 1997). Random assignment of study subjects to treatments minimises the risk of selection bias, i.e. the risk for systematic differences between the comparison groups at baseline (ICH harmonized tripartite guideline 1998, Higgins and Altman 2008, Finnish Medical Society Duodecim 2012). Blinding the subjects and study personnel for the study assignment minimises the risk for the knowledge on the type of the assignment causing the observed effects instead of the assigned intervention itself (Higgins and Altman 2008). Furthermore, given the appropriate randomization procedure and blinding, the application of the intention to treat principle also minimises bias as it maintains the comparability of the study groups by accounting for deviations from the treatment assignment during study conduct and assuring that all randomised subjects are included in the primary analysis (Bornhöft *et al.* 2006, Higgins and Altman 2008, Finnish Medical Society Duodecim 2012). Similarly, there are means to maintain patient compliance (i.e. adherence, see section 2.2.3.3) during the trial which further strive to minimise bias arising from such issues (ICH harmonized tripartite guideline 1997, Finnish Medical Society Duodecim 2012). Additionally, the selection of a homogenous trial population is an integral part of minimizing bias in RCTs (Rothman *et al.* 2013). The strict trial inclusion and exclusion criteria may, however, limit the external validity of the trial results or the representativeness of the trial characteristics for real-world clinical care (Rothwell 2005, Atkins *et al.* 2011). This has also been shown to commonly be the case (Britton *et al.* 1999, van Spall *et al.* 2007, Jadad *et al.* 2011). For example, the proportions of real-world patients with atrial fibrillation and deemed eligible in the UK to participate in the pivotal RCTs on novel oral anticoagulants varied from 48% to 64% (Lee *et al.* 2012). Similarly, the proportion of patients with type 2 diabetes living in Scotland and deemed eligible for the UKPDS was 32%–51% and 4%–36% for various other RCTs on intensive glucose lowering therapies (Saunders *et al.* 2013).

The term "external validity" (Jadad *et al.* 2011, Rothwell 2005) of the trial results refers to "the extent to which the effects observed in published studies are likely to reflect the expected results when a specific intervention is applied to the population of interest under real-world conditions" (Atkins *et al.* 2011). External validity may also be defined terminologically as directness (Guyatt *et al.* 2008), generalizability (ICH harmonized tripartite guideline 2012) or applicability (Atkins *et al.* 2011, Dans *et al.* 1998, Fahey 1998, Gorenoi *et al.* 2011, Mangoni *et al.* 2006). In this thesis the term applicability will be used as proposed by the Agency for Healthcare Research and Quality to cover the variety in the nomenclature (Atkins *et al.* 2011).

The representativeness of the trial characteristics for real-world clinical care is considered as a basic requirement when one considers the applicability of the trial findings (Atkins *et*

al. 2011).The basic design features considered to affect the representativeness of the trials for real-world clinical care are presented in Table 2.7 according to the PICOS approach (i.e. **P**atients, **I**nterventions, **C**omparators, **O**utcomes and **S**etting).

Table 2.7. Features affecting the representativeness of randomised controlled trials for real-world clinical care according to the PICOS approach (based on Atkins *et al.* 2011, Bornhöft *et al.* 2006 and Rothwell 2005).

Patients	Socio-demographic characteristics (age, sex, racial group, ethnicity)
	Severity and duration of illness
	Comorbidities
	Concomitant medications
	Therapy preferences and expectations
	Prior response to relevant therapies
	Symptoms of adverse events and adverse drug reactions (i.e. an active treatment run-in period applied before randomisation and the proportion of patients excluded due to intolerance of the treatment)
	Adherence to treatment (i.e. an active treatment or placebo run-in period applied before randomisation and the proportion of patients excluded due to poor adherence)
	The applied inclusion and exclusion criteria
	Prerandomisation diagnostic procedures
	The applied diagnostic criteria
	Experience and background of the persons performing the diagnostic procedures
	The baseline risk for poor outcome as a prognostic factor in the control group
	Recruitment of volunteers or recruitment from primary, secondary or tertiary care units
Interventions	Preparation
	Route of administration
	Dose and dose modification
	Schedule and duration of dosing
	Methods to promote adherence
	Allowed accompanying treatments
	Qualification and experience of the persons administering the intervention
	Intensity, delivery and feasibility of concurrent behavioural interventions
Comparator	Clinical relevance
	Dose and schedule
	Monitoring

Outcome	Clinical relevance
	Variations in the clinical relevance of the events combined in a composite outcome
	Clinical relevance, validity, and reproducibility of complex scales
	Sensitivity to establish efficacy
	Patient-centeredness (quality of life, mortality)
	Test procedures used to define the outcome of interest
	The qualification and professional experience of the persons defining outcomes
Setting	Study years
	Geographical site of the participating centres
	Frequency and type of follow-up procedures
	Safety procedures
	Length of follow-up
	Assessment of adherence and adverse events
	The experience, training and number of contact persons
	Drop-out rate
	Reasons for drop-outs

In general, RCTs have been criticized for prioritising internal validity at the expense of applicability and representativeness (Britton *et al.* 1999, van Spall *et al.* 2007; Jadad *et al.* 2011). Furthermore, the legislations and rules governing the conduct of premarketing RCTs, i.e the Good Clinical Practice guidelines (ICH 1996) and the Declaration of Helsinki (available at www.wma.net), have also been criticized for not considering the external validity of the trial results (Rothwell 2005). In addition, the clinical statin trials have been shown to be under-representative for real-world clinical care, in particular having poor representation of women and the elderly, (Barttlet *et al.* 2005, Wei *et al.* 2005, Konrat *et al*. 2012, Bandyopadhyay *et al*. 2001). Nonetheless, previous studies on the representativeness of statin trials have focused only on limited demographic characteristics such as age and gender. Consequently, a systematic review assessed the representativeness of the placebo controlled statin RCTs published from 1990 to 1999 (N=19) and found that 81% of the trial subjects were male (Bandyopadhyay *et al*. 2001) and only one study with inconclusive trial findings included subjects also aged beyond 75 years (Bandyopadhyay *et al*. 2001, Furberg *et al.* 1994). Another review assessed the representativeness of 27 statin RCTs with at least 6 months of duration (up to August 2001) and in which all patients had previously had major CVD events (Barttlet *et al.* 2005). The mean age of the trial subjects was 59 years and 16% were women. In comparison, women constituted 45% of the potential population in need of statin therapy in England, and of these, two thirds were aged 65 years or more, as assessed from administrative registers. Likewise, only three out of 29 rosuvastatin RCTs were found to have the proportion of trial subjects aged 65 or older similar to or higher than the appropriate French population taking statins in clinical practice (Konrat *et al*. 2012).

When treating patients, physicians have applied the knowledge derived from the clinical statin trials with inherent limitations in representativeness yet showing statin efficacy under controlled circumstances. It has been feared, that the limited representativeness of

the trial participants would lead to denial of effective treatments from those underrepresented in the trials yet likely to benefit from the therapy (Britton *et al.* 1999). However, there is a trade-off which needs to be made in increasing the representativeness of the trials for real-world clinical care: without a homogenous trial population, the internal validity of the trial results may be questioned, the conclusions from a trial are more likely to be wrong, and therefore, the representativeness of a trial would be irrelevant (Elwood 2013). On the other hand, the efficacy in a RCT does not automatically translate into effectiveness. This thesis distinguishes between the terms "efficacy" and "effectiveness" in a way clinicians and policymakers often do: efficacy refers to whether an intervention produces the expected result under the ideal circumstances of RCTs and effectiveness refers to the degree of the intended beneficial effects under "real-world" clinical care (Gartlehner *et al.* 2006).

2.2.3 Pharmacoepidemiology of statins

2.2.3.1 Data sources

Although pharmacoepidemiological studies apply various available data sources, the use of databases of routinely collected healthcare information has expanded during the last decade (Hall *et al.* 2012). Administrative databases may refer to administrative records primarily constructed for administrative purposes that include data on reimbursed prescriptions, professional health services, and hospitalizations etc. Furthermore, electronic medical records may also contain detailed clinical information such as the findings of physical examinations, and the results of diagnostic tests maintained for the purpose of clinical care (Schneeweiss and Avorn 2005). There are several terms used for these databases exploited in observational research but actually collected for other purposes e.g. observational datasets, linked databases, data resources and multi-purpose databases, the latter term being introduced only recently (Hall *et al.* 2012). The studies included in this thesis all utilised administrative databases of routinely collected, administrative healthcare information which are referred to as administrative registers below.

2.2.3.2 Use of statins in human populations

"The ultimate goal of drug utilisation research must be to assess whether drug therapy is rational or not" (WHO 2003). Various pharmacoepidemiological studies and drug consumption statistics have shown that the use of LLDs, mainly statins, has markedly increased in western societies (Martikainen *et al.* 1996, Baxter *et al*. 1998, Larsen *et al.* 2001, Mantel-Teeuwisse *et al.* 2002, Nordic Medico Statistical Committee 2004, Raymond *et al.* 2007) and also in Finland (Figure 2.2). This was primarily triggered by the outcomes of the 4S in 1994 (Scandinavian Simvastatin Survival Study Group 1994) and further by the publication of other benchmarking statin trials in the late 1990s, i.e. the WOSCOPS (Shepherd *et al.* 1995), the CARE (Sacks *et al.* 1996) and the LIPID studies (Long-Term Intervention with Pravastatin in Ischemic Disease Study Group 1998). The increases in statin therapies have been reflected in both the incidence and prevalence of use (Mantel-Teeuwisse *et al*. 2002, Larsen *et al.* 2001, Riahi *et al.* 2001), both of which are measures considered as fundamental for drug utilisation research (Hallas 2005). Furthermore, population-based prescription databases with records on individual statin dispensing and unique person identifiers have made it possible to gather individual level drug statistics, e.g. those that are categorized by gender and age (Larsen *et al.* 2001, Mantel-Teeuwisse *et al.* 2002, Riahi *et al.* 2001). Hence, it has been reported, that the median age of statin users during the late 90s and at the beginning of the 21st century was 60 to 70 years and statin users were predominantly male (Larsen *et al.* 2001, Mantel-Teeuwisse *et al.* 2002, Riahi *et al.* 2001, Sakshaug *et al.* 2007). Concordant with prevalence, the majority of incident statin users were male and aged around 60 to 70 years (Larsen *et al.* 2001, Mantel-Teeuwisse *et al.* 2002, Riahi *et al.* 2001). The proportion of females among the initiators had increased from the early to the late 90s (Larsen *et al.* 2001, Riahi *et al.* 2001) while underuse of statins among the elderly was feared for (Gaw 2004).

More recently, a decline in the incidence of statin use has been noted. In Israel, the number of incident statin users increased from the year 2000, peaked in 2005 but declined by half by the year 2010 among all age groups except for those aged 30 to 44 years (Shalev *et al.* 2014). In the Netherlands, the incidence from 1999 to 2008 peaked in 2006 among those aged 50 to 79 years declining subsequently, whereas the incidence continued to increase in the oldest age group of those aged 80 years or more (Geleedst-De Vooght *et al.* 2010). In Israel, the mean age at statin initiation decreased from 59 years to 55 years from 2000 to 2010, with a similar decreasing trend noted in both men and women (Shalev *et al.* 2014). However, women were found to be three years older, on average, than men at statin initiation and also with a higher baseline LDL cholesterol level. Simultaneously, the mean LDL cholesterol level at statin initiation decreased from 4.2 mmol/L to 4.0 mmol/L and the proportion of patients presenting with prior CHD decreased from 18% to 7% but that of patients with diabetes increased from 9% to 16% (Shalev *et al.* 2014). Almost half i.e. 48%, of statin initiators were women in the year 2000 in Israel, the respective proportions were 52% in 2005 and 46% in 2010 (Shalev *et al.* 2014).

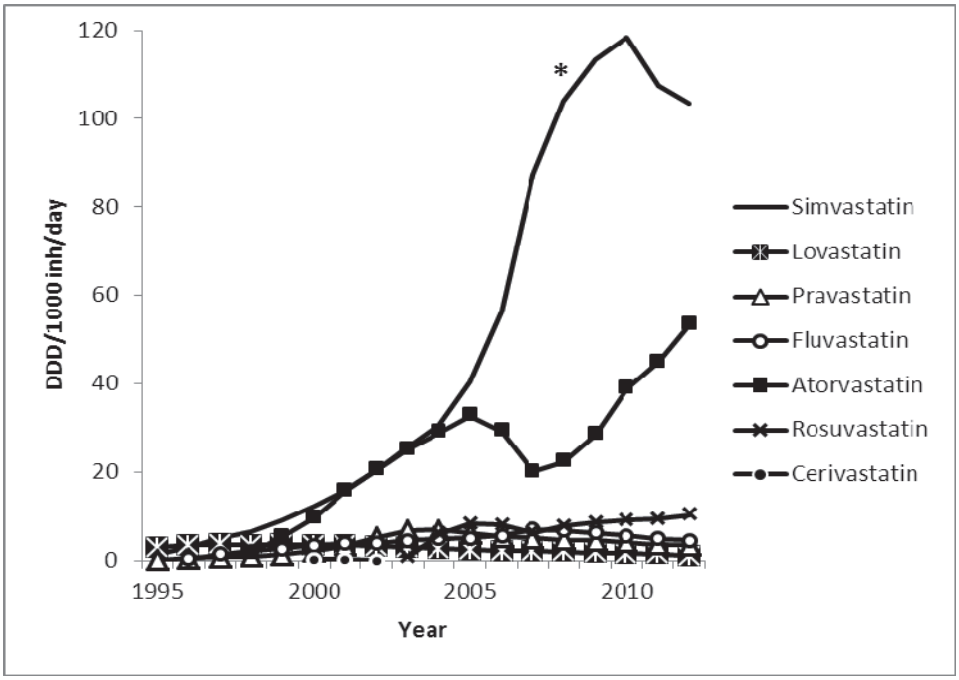

Figure 2.2. Consumption of statins in Finland in 1995─2012 (Based on Finnish Statistics on Medicines in 1995─2012). The consumption statistics are based on calculations using the volume of sales to pharmacies and hospitals by wholesalers divided by the assumed average dose per day for each statin as expressed by the unit Defined Daily Dose (DDD) assigned by the WHO (The World Health Organization Collaborating Centre for Drug Statistics Methodology, 2013). *To allow between year comparisons, the DDDs valid for the years 1995-2007 (simvastatin 15mg, lovastatin 30mg, pravastatin 20mg, fluvastatin 40mg, atorvastatin 10mg, rosuvastatin 10mg) were also applied for the years 2008-2012, despite the change in their DDD values (The National Agency for Medicines and The Social Insurance Institution. Finnish Statistics on Medicines 1995-2012. Helsinki, Finland: 1996-2013).

2.2.3.3 Adherence to statins

There are a number of terms used in the scientific literature to define appropriate medicine taking behavior in clinical practice. Commonly, the terms "compliance", "adherence","persistence" and "concordance" are used (Vrijens *et al.* 2012). Although each refers to a distinct approach to drug utilisation behavior, the terms seem to overlap in the scientific literature describing deviations from prescribed treatments (Vrijens *et al.* 2012). In this thesis, the term "good adherence" refers to patients taking their purchased medications as prescribed by the physician. An arbitrary, but widely used, cut-off point for good adherence has been 80% or more for the proportion of days covered (PDC, see Methods) with therapy during the follow-up period or for the medication possession ratio (MPR, see Methods) (Benner *et al.* 2002, Schneeweiss *et al.* 2007, Perreault *et al.* 2009a, Perreault *et al.* 2009b). Adherence of at least 80% corresponds to the cut-off point for adherence typically regarded as appropriate in clinical trials (Osterberg and Plaschke 2005), for example, it does permit not taking the prescribed daily dose once every week.

Despite the growth in the incidence and prevalence of statin use in the western societies, suboptimal adherence to statins may decrease the full benefit in actual clinical care. Furthermore, the ability of the physicians to recognize poor adherence is limited whereas subjects in RCTs are supervised to ensure adequate adherence to the study treatments (Osterberg and Blaschke 2005). Correspondingly, some statin trials have reported that adherence below 80% has been applied as a trial exclusion criterion (Colhoun *et al.* 2004, Knopp *et al.* 2006, Ridker *et al.* 2008). In real-world, however, there are many patients with less than 80% adherence to statin therapy (Mantel-Teeuwisse *et al.* 2004, Perreault *et al.* 2005, Benner *et al.* 2002), a situation also found in Finland (Helin-Salmivaara *et al.* 2008). Depending on the conducted meta-analysis, 54% of all patients or 57% of those without established CVD and 76% of those with CVD were considered to be adhering appropriately to their statin therapy over a two or three year observation period with the appropriate adherence defined either as a PDC or MPR of ≥75% or ≥ 80% (Naderi *et al*. 2012, Chowdhury *et al.* 2013).

Several patient-related, physician-related and health system-related factors influence adherence behaviour (Maningat *et al.* 2013). Non-adherence may arise from low social status, suboptimal health literacy, lack of involvement in treatment decision-making, comorbidity and subsequent polypharmacy, communication barriers, uncertainty about the drug effectiveness, serious adverse events occurring during therapy, limited access to care, lack of health information technology and high copayments (Brown and Bussell 2011, Maningat *et al.* 2013). Additionally, the age of the patient plays a role in adherence to statins although this is not linear: non-adherence is more common both among those aged 50 years or less and among the elderly (Mann *et al.* 2010). Additionally, heavy alcohol consumption and clustering of unhealthy habits seem to associate with non-adherence in patients with established CVD (Halava *et al.* 2014). For those without previous CVD, however, obesity and former smoking seem to combat against non-adherence to statin use (Halava *et al*. 2014). For comparison, good adherence is consistently associated with male gender, frequent lipid testing, the presence of previous CVD events, hypertension and

diabetes supporting the relationship between perceived CVD risk and adherence (Helin-Salmivaara *et al.* 2008, Mann *et al* 2010, Latry *et al.* 2011, Lemstra *et al.* 2012).While hypertension and diabetes lower the odds of non-adherence to statins by approximately 10% in comparison with those not presenting with these features, the presence of CVD lowers the odds by 30% (Mann *et al.* 2010). Furthermore, patients with good adherence to statins seem also to behave in an otherwise healthier manner, making them less susceptible for adverse events. In the US and Canada, patients with good adherence to statins were likely to seek various screening services and vaccinations more often and experienced fewer motor vehicle accidents and workplace accidents than those with lower statin adherence (Brookhart *et al.* 2007, Dormuth *et al.* 2009). Similarly, in comparison with clinical trial participants with poor adherence to placebo, participants with good placebo adherence have a reduced risk for all-cause death and CVD mortality (Simpson *et al.* 2006, Yue *et al.* 2014). Nonetheless, even in diabetes, adherence to statin therapies in clinical practice is lower than that achieved in the clinical statin trials: It seems that the mean PDC during the first year of use is high (87%) but decreases subsequently to an average level of 60% (Donnelly *et al.* 2008). Overall and also in diabetes, the majority of initial statin doses have corresponded to simvastatin equivalent doses of less than 40 mg (Donnelly *et al* 2008, Eliasson *et al.* 2011, Kiviniemi *et al.* 2011, Leiter *et al.* 2011, Simpson *et al.* 2013), and 10 to 20% of patients with diabetes seem to use simvastatin equivalent doses of less than 20 mg (Eliasson *et al.* 2011, Beard *et al.* 2013). In addition, the up-titration of statin doses seems to be suboptimal even among patients with a high background risk for future CVD events (Foley *et al.* 2003, Kiviniemi *et al.* 2011, Simpson *et al.* 2013, Arnold *et al.* 2014). The result may be a lower statin exposure and suboptimal effectiveness of statin therapy in clinical practice as compared to the situation in the clinical trials.

2.2.3.4 Effectiveness of statins in human populations

The rationale to conduct observational, pharmacoepidemiological cohort, case-control or cross-sectional statin studies using administrative databases reflects the general limitations of data retrieved from randomised controlled trials (Table 2.8). As opposed to the confirmatory, strictly controlled statin trials, pharmacoepidemiological statin studies have the advantage of minimizing the amount of exclusion criteria in the study population and are, thus, able to include diverse patient groups with varying degrees of disease severity, varying comorbidities and concomitant medications (Atar *et al.* 2012 Atkins 2007, Bornhöft *et al.* 2006, MacMahon and Collins 2001, Rothwell 2005, Yang *et al.* 2010).

Table 2.8. The advantages of randomised controlled trials and observational studies using large administrative databases (based on Atar *et al.*2012, Atkins 2007, Bornhöft *et al*. 2006, MacMahon and Collins 2001, Rothwell 2005 and Yang *et al.* 2010)

	RCTs	**Observational studies**
Patients	Well defined, homogenous study populations	Large study populations representative for all relevant patient groups
Interventions	Designed to maximize the average treatment effect Treatment effects as consequences of optimal adherence to study treatment Administered to well defined treatment groups	Allow for investigating the real-world average treatment effect Allow for investigating the consequences of varying levels of adherence to treatment Allow for investigating the consequences of switching between available treatments Allow for investigating targeting of therapy and prescribing preferences
Comparators	Placebo comparison isolates the effect of study treatment Active treatment comparison allows for differentiating between treatment effects	Representative for usual care
Outcomes	Well defined and detected Reliable data on the incidence of common adverse events	Large study populations and long follow-up periods allow for investigating outcomes of clinical relevance Allow for investigating the occurrence of rare or slow emerging serious adverse events
Settings	Tightly controlled and monitored	Real-world conditions, with variation in practice depending on physician's clinical judgment of individual patients
Other	Randomisation allows for homogeneity and comparability between groups Double -blinding allows for comparability in study performance between groups Intention-to-treat analysis allows for comparability between groups and for protocol deviations	
Interpretation	Efficacy and safety (under ideal conditions)	Beneficial and adverse effects under real-world conditions

Several administrative register based studies have assessed the degree of the beneficial statin effects in real-world CVD prevention. With respect to the incidence of CHD events, a non-significant decrease was observed for statin initiators versus non-initiators (HR 0.89, CI 0.73- 1.09) among 75 000 individuals without previous CVD and with 650 subsequent CHD events observed during an average follow-up time of 2,3 years (Danaei *et al.* 2013). When non-adherence to statin therapy during follow-up was accounted for, the HR remained essentially the same (HR 0.84, CI 0.54- 1.30). In another study, with data from more than 8000 individuals both with and without prior CVD and in whom there were less than 200 subsequent events observed during a maximum follow-up time of 4,5 years, the relative rate of acute myocardial infarction among statin-initiators decreased by as much as 30% when compared to non-initiators (HR 0.69, CI 0.52-0.93) (Seeger *et al.* 2003). In other cohort studies with larger study populations and higher numbers of events and with follow-up times of 2 to 4 years, a wider range of clinical outcomes have been assessed (Smeeth *et al.* 2009, Sheng *et al.* 2012a). Correspondingly, statistically significant decreases in event rates associated with statin use among patients presenting both with and without prior CVD were observed for CVD related outcomes: the HR for all-cause mortality was 0.79-0.89, HR for MI 0.81-0.87 and HR for stroke 0.85-0.88. In a subgroup of patients with diabetes, similar or somewhat larger reductions in the incidence of these CVD events have been observed to associate with statin use for all except for the incidence of stroke among those with diabetes and prior CVD (Sheng *et al.* 2012b).

While the majority of the studies comparing statin use versus non-use did not account for the various levels of adherence to statins (Seeger *et al*. 2003, Smeeth *et al.* 2009, Sheng *et al.* 2012), several studies have assessed the association between adherence to statin use and the incidence of CVD events (Table 2.9). As compared to lower adherence, the reductions in the incidence of various CVD events associated with high level of adherence (≥ 80%), have been similar but also considerably larger than those in the above studies on statin use versus non-use. At the meta-analysis level, good adherence to statins defined as PDC ≥ 80% was associated with a 15% reduction in the relative risk of CVD events and with a 45% reduction in the relative risk of all cause mortality during a mean follow-up of 3.2 years (Chowdhury *et al.* 2013). However, adherence to statin therapy among patients with diabetes differs from that of their non-diabetic peers (Naderi *et al.* 2012, Latry *et al.* 2011, Helin-Salmivaara *et al.* 2008) and the background risk for CVD events is higher in patients with diabetes (Haffner *et al.* 1998, Schramm *et al.* 2008, Kuusisto and Laakso 2013). Although the higher backround CVD risk in diabetes has not been shown to modify the relative treatment effect of statins on CVD (Cholesterol Treatment Trialists' Collaboration 2010) it is important to evaluate whether the varying adherence to statins is associated with differences in the relative risk of hard CVD events among this patient group. The available data evaluating this issue are described in Table 2.10.

Table 2.9. The association between statin adherence and a selection of clinical consequences in administrative register based pharmacoepidemiological studies.

Study	Number of patients	DM (%)	Adherence measures	Main outcome measures from the adjusted multivariable analysis	Other relevant outcome measures	Results available for patients with diabetes	Setting
Study population without CVD							
Bouchard *et al.* 2007	20,543	19	PDC <90% (reference) vs. ≥90%	CAD events: RR 0.92 (CI 0.82–1.03)	CAD events: RR 0.81 (CI 0.67–0.97)	No	Régie de l'assurance maladie du Québec database, Canada
Perreault *et al.* 2009a	115,290	26	MPR <20% (reference) vs. >80%	NA for the whole cohort	CAD events: RR 0.82 (CI 0.77–0.87)	No	Régie de l'assurance maladie du Québec database, Canada.
Perreault *et al.* 2009b	112,092	21	MPR, <20% (reference) vs. ≥80%	NA for the whole cohort.	Cerebrovascular disease events: RR 0.74 (CI 0.65–0.84) Ischemic stroke: RR 0.67 (CI 0.58–0.77)	Yes	Régie de l'assurance maladie du Québec database, Canada.
Corrao *et al.* 2010	90,823	18	PDC ≤25% (reference) 26–50% 51–75% >75%	IHD events: HR 0.85 (CI 0.72–0.98) HR 0.82 (CI 0.71–0.95) HR 0.81 (CI 0.71–0.94)		No	Health service database of Lombardy, Italy

Table 2.9. The association between statin adherence and a selection of clinical consequences in administrative register based pharmacoepidemiological studies. *(Continued)*.

Study	Number of patients	DM (%)	Adherence measures	Main outcome measures from the adjusted multivariable analysis	Other relevant outcome measures	Results available for patients with diabetes	Setting
Study population without CVD							
Dragomir *et al.* 2010	55,134	31	MPR < 80% (reference)* vs. ≥80%	All-cause hospitalization: OR 0.96 (CI 0.92–0.99)	CAD events: OR 0.93 (CI 0.88–0.99) Cerebrovascular disease events: OR 0.88 (CI 0.80–0.97) HF: OR 0.88 (CI 0.79–1.26)	No	Régie de l'Assurance Maladie du Québec and Med-Echo databases, Canada.
Shalev *et al.* 2012	171,535	4,5	PDC <20% (reference) 20–40% 40–60 60–80% >80%	MCEs for women: HR 0.93 (CI 0.82–1.05) HR 0.71 (CI 0.63–0.80) HR 0.57 (CI 0.51–0.65) HR 0.59 (CI 0.53–0.66) For men: HR 0.95 (CI 0.87–1.03) HR 0.75 (CI 0.69–0.81) HR 0.64 (CI 0.59–0.69) HR 0.60 (CI 0.56–0.64)	CVD events for all: HR 0.90 (CI 0.85–0.96) HR 0.71 (CI 0.67–0.75) HR 0.63 (CI 0.59–0.67) HR 0.64 (CI 0.60–0.67) MI events for all: HR 0.75 (CI 0.67–0.84) HR 0.54 (CI 0.48–0.61) HR 0.42 (CI 0.38–0.47) HR 0.39 (CI 0.35–0.43)	Yes	Maccabi Healthcare Services database, Israel

Study population with CVD							
Wei *et al.* 2002	5163	NA	No statin use (reference) PDC <39% PDC 40–79% PDC ≥80%.	All-cause mortality: RR 0.94 (CI 0.39–2.27) RR 1.15 (CI 0.44–3.00) RR 0.47 (CI 0.22–0.99)	NA	No	Medicine Monitoring Unit's record linkage Database, Tayside, Scotland.
Blackburn *et al*. 2005	1056	27	Number of prescriptions filled divided by the number of months of observation ≤ 60% (reference) vs. ≥ 80%.	CAD events and all-cause mortality: HR 0.87 (CI 0.61–1.26)	MI: HR 0.45 (CI 0.20–0.99)	No	Several administrative health databases in Saskatchewan, Canada.
Ho *et al.* 2006a	2833	100	Summary PDC for ≥1 CVD medications (including statins) < 80% (reference) vs. ≥80%	All-cause mortality: OR 0.52 (CI 0.39–0.69)	All-cause mortality separately for statins: OR 0.59 (0.41–0.87)	Yes	Kaiser Permanente database of Colorado, USA.

Table 2.9. The association between statin adherence and a selection of clinical consequences in administrative register based pharmacoepidemiological studies. *(Continued).*

Study	Number of patients	DM (%)	Adherence measures	Main outcome measures from the fully adjusted multivariate analysis	Other relevant outcome measures	Results available for patients with diabetes	Setting
Study population with CVD							
Rasmussen *et al.* 2007	17,823	3,5	PDC < 40% (reference)* 40–79% ≥80%	All-cause mortality: HR 0.89 (CI 0.80–0.99) HR 0.80 (CI 0.70–0.92)	NA	No	Ontario Myocardial Infarction Database, Canada.
Ho *et al.* 2008	13,596	36	PDC <0.80 (reference)* vs. ≥0.80	All-cause mortality: HR 0.54 (CI 0.48–0,61) CVD mortality: HR 0.62 (CI 0.47–0.81)	AMI or HF: HR 0.74, (CI 0.67–0.83) Coronary revascularization: HR 0.90 (CI 0.82–0.99)	No	Kaiser Permanente database of Colorado, USA.
Wei *et al.* 2008	671	NA	PDC < 80% (reference) vs. ≥80%	CVD events: RR 0.66 (CI 0.47–0.91)	All-cause mortality: RR 0.72 (CI 0.42–1.24)	No	Medicine Monitoring Unit's record linkage Database, Tayside, Scotland.
Tuppin *et al.* 2010	10,501	25	PDC < 80% (reference)* vs. ≥80%	All-cause mortality and hospitalization for CAD: HR 0.63 (CI 0.55–0.73)	NA	No	Système national d'informations inter-régimes de l'assurance maladie and Programme de medicalization des systèmes d'information, France.

Allonen *et al.* 2012	1969	23	Irregular statin use (dispense interval >180 days, reference) vs. regular use (dispense every 180 days)*	All-cause mortality HR 0.65 (CI 0.45–0.94)	NA	No	Genetic Predisposition of Coronary Artery Disease (Corogene) register, Prescription Register, Causes of Death Register, Finland
Study population with and without CVD							
Ho *et al.* 2006b	6486	100	PDC <80 (reference)* vs. ≥80%	All-cause hospitalization: OR 0.72 (CI 0.61– 0.85) All-cause mortality: OR 0.48 (CI 0.36–0.65)	NA	Yes	Kaiser Permanente database of Colorado, USA.
Shalev *et al.* 2009	136,052 (without CVD), 93,866 (with CAD).	25, 31	PDC < 10% (reference) vs. ≥90%.	All–cause mortality for patients without prior CVD: HR 0.55 (CI 0.49–0.61) All–cause mortality for patients with prior CAD: HR 0.49 (CI 0.46–0.53)	NA	No	Maccabi Healthcare Services database, Israel.

Table 2.9. The association between statin adherence and a selection of clinical consequences in administrative register based pharmacoepidemiological studies. *(Continued).*

Study	Number of patients	DM (%)	Adherence measures	Main outcome measures from the fully adjusted multivariate analysis	Other relevant outcome measures	Results available for patients with diabetes	Setting
Study population with and without CVD							
Poluzzi *et al.* 2011	137,217	16	See footnote[1*]	CVD events: OR 1.05 (CI 1.05–1.06) OR 1.42 (CI 1.34–1.44) OR 0.84 (CI 0.81–0.87)	NA	Yes	Emilia– Romagna Regional Health Authority Database, Italy.
Degli Esposti *et al.* 2012	19,232	18	PDC 21– 40% (reference) 41–60% 61–80% >80%.	All–cause mortality, AMI or stroke: HR 0.83 (CI 0.71–0.98) HR 0.60 (CI 0.51–0.70) HR 0.61 (CI 0.54–0.71)	AMI: HR 0.99 (CI 0.66–1.47) HR 0.82 (CI 0.56–1.21) HR 0.79 (CI 0.56–1.10) Stroke: HR 0.77 (CI 0.58–1.01) HR 0.65 (CI 0.50–0.84) HR 0.73 (CI 0.58–0.90)	No	Several databases of the Local Health Unit of Florence, Italy.
Haukka *et al.* 2012	683236	7.8	No statin use (ref) vs. Adherence 80%	All cause moratlity RR 0.42 (CI 0.37–0.47)	CHD mortality RR 0.54 (CI 0.46–0.64)	No	Prescription Register, National Hospital Discharge Register, Causes of Death Register, Finland

Rublee *et al.* 2012	79,010 (without CVD) 15,277 (with CVD)	23	Non-adherence (reference): no tablet coverage during the 90 days at the end of a 1–year assessment period and/or PDC < 60%. Definition for adherence NA.	CVD events for patients without prior CVD: HR 0.82 (CI 0.74–0.91) CVD events for patients with prior CVD: HR 0.74 (CI 0.66–0.82)	NA	No	The InVision Data Mart database, USA.

*For the purposes of comparison, the original reference group was switched and the corresponding reciprocal was calculated for the main outcome measure. [1] Strong non–adherence: < 200 tabl/y (reference), Slight non–adherence: ≥200, <300 tabl/y, Highly variable adherence: differences of ≥ 200 tablets/y between years, Adherence: ≥ 300 tabl/y received in 3 years.Abbreviations: AMI= acute myocardial infarction; CAD= coronary artery disease; CI= 95% confidence interval; CVD= cardiovascular disease; DM=diabetes mellitus; HF= heart failure; HR= hazard ratio; IHD= ischemic heart disease; MI=myocardial infarction; MCE= major coronary event; NA= not available; OR= odds ratio; PDC= Proportion of days covered; RR= relative risk; MPR= Medication possession ratio. Patients with diabetes refer to patients with established diagnosis for diabetes and/or users of antidiabetic drugs.

Table 2.10 Design features and basic characteristics of the administrative register based pharmacoepidemiological studies on statin adherence and clinical consequences in diabetes.

		Baseline characteristics of patients with diabetes on statin therapy									
Study: First author, year		**Number of patients**	**CVD (%)**	**Age (y)[1]**	**Male (%)**	**Type 1 diabetes (%)**	**Duration of diabetes (y)[1]**	**HT (%)**	**TC (mmol/l)[1]**	**HbA1c (%)[1]**	**Current smoking (%)**
Perreault *et al.* 2009b*		NA	0	NA	NA	NA	NA	NA	NA	NA	NA
	Design features [2]	A nested case–control design where eligible patients initiated statin use between Jan 1999 and Dec 2004 (no LLDs in the preceding 2 years), were aged 45–85 years and had no CVD as indicated by the absence of a related diagnosis or medical procedure in the 5 years, and a drug marker in the 2 years before statin initiation. Cases and controls were matched according to age at cohort entry (±1y) and the length of follow-up. The mean follow-up time was 2.95y.									
	Variables[3]	Sex and social assistance at statin initiation, occurrence of CVD conditions, use of antiplatelet drugs and an updated patient chronic disease score during follow-up, and hypertension and diabetes in the year before statin initiation and during follow-up (categorized into those never treated and those treated with adherence to treatment in the last year of follow-up dichotomized into < 80% and >80%).									
	Outcome of interest	Incidence of cerebrovascular disease events including intracerebral haemorrhage, occlusion and stenosis of precerebral arteries, occlusion of cerebral arteries, acute cerebrovascular disease but ill-defined cerebrovascular disease and other ill-defined cerebrovascular disease.*									
	Outcome measures	A subgroup analysis on patients with diabetes and/or with hypertension: RR 0.71, 95% CI 0.60–0.83 for MPR <20% (ref) vs. MPR>80%									

Shalev *et al.* 2012		33,668	0	NA	NA	NA	NA	NA	NA	NA	NA
	Design features [2]	A cohort design where eligible patients initiated statin use between 1998 and 2007 (no statin drugs in the preceding 3 years), were aged 45–75 years, presented without prior CVD, survived at least 1 year after statin initiation and were without large amounts of statins (15% above the amount required for complete coverage). All analyses were stratified by gender. The mean follow-up time was 6.0y form women and 5.5y for men.									
	Variables[3]	Statin efficacy (accounting for cumulative doses, prescription days and statin type as simvastatin equivalent doses) and baseline characteristics including age, gender, residential socioeconomic level, diabetes mellitus, hypertension, use of health services and median baseline lipid levels in the year before statin initiation.									
	Outcome of interest	Incidence of MCEs including MI, percutaneous coronary intervention and coronary artery bypass grafting.*									
	Outcome measures	A subgroup analysis: HR 0.52, 95% CI 0.43–0.62 (women), HR 0.50, 95% CI 0.44– 0.57 (men) for PDC <20% (ref) vs. PDC>80%. MI: HR 0.40 (CI 0.30– 0.54) (women) HR 0.34 (CI 0.27–0.43) (men) for PDC <20% (ref) vs. PDC>80%.									

Table 2.10 Design features and basic characteristics of the administrative register based pharmacoepidemiological studies on statin adherence and clinical consequences in diabetes. *(Continued).*

Study: First author, year		**Number of patients**	**CVD (%)**	**Age (y)[1]**	**Male (%)**	**Type 1 diabetes (%)**	**Duration of diabetes (y)[1]**	**HT (%)**	**TC (mmol/l)[1]**	**HbA1c (%)[1]**	**Current smoking (%)**
Ho *et al.* 2006a*		2833	100	NA	NA	NA	NA	NA	NA	NA	NA
	Design features [2]	A cohort design where eligible patients with diabetes and IHD were aged ≥18 years and were in the register from Sep 2002 until Dec 2003. The mean follow-up time was NA (min 90d, max 365d).									
	Variables[3]	Sex, age, hypertension, prior MI, PAD, cerebrovascular disease, COPD, HF, sleep apnea, renal insufficiency, retinopathy, hypercholesterolemia, blood pressure, LDL cholesterol and HbA1c at baseline.									
	Outcome of interest	All-cause mortality.									
	Outcome measures	OR 0.59, 95% CI 0.41–0.87 for PDC <80% (ref) vs. PDC ≥80%									
Ho *et al.* 2006b*		6486	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Design features [2]	A cohort design where eligible patients with diabetes were aged ≥18 years and were in the register from Sep 2002 until Dec 2003. The outcomes were identified from Jan 2004 through Apr 2005. The mean follow-up time was 1,3y.									
	Variables[3]	Sex, age, hypertension, prior MI, CAD, PAD, cerebrovascular disease, COPD, HF, sleep apnea, renal insufficiency, retinopathy, hypercholesterolemia, diet-controlled diabetes, oral hypoglycemics only, insulin only, insulin and oral hypoglycemics, no. of antihypertensives, no. of oral hypoglycemics, blood pressure, LDL cholesterol and HbA1c at baseline.									
	Outcome of interest	Incidence of all-cause hospitalization and all-cause mortality.									
	Outcome measures	All–cause hospitalization: OR 0.72, 95% CI 0.61– 0.85 for PDC <80% (ref) vs. PDC ≥80%. All–cause mortality: OR 0.48 (CI 0.36–0.65) for PDC <80% (ref) vs. PDC ≥80%.									

Poluzzi *et al.* 2011		21,530	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Design features [2]	A case–control design where eligible patients received at least one reimbursed statin prescription between Jan and Feb 2005 and at least another statin prescription during the first year of follow-up and survived a 3-year follow-up period. Subsequently, the follow-up time was 3y for all.									
	Variables[3]	Age, sex, comorbidity (diabetes, hypertension, angina, heart failure and thrombosis) in the first year of follow-up.									
	Outcome of interest	Incidence of CVD events including IHD, cerebrovascular disease, atherosclerosis, PAD, arterial embolism or thrombosis*									
	Outcome measures	A subgroup analysis: OR 1.36, 95% CI 1.31–1.40 for ≥ 300 tablets/y received in 3 years (ref) vs. <300 tablets/y received.									

*For subgroup analysis the outcome is defined as published for the main analysis. [1]Presented as mean values unless otherwise stated. [2] With special emphasis on methods to control for measured confounding. [3]Covariates included in the main multivariable analysis. Abbreviations: ACE=angiotensin-converting enzyme; CAD=coronary artery disease; COPD= chronic obstructive pulmonary disease; CVD= cardiovascular disease; HbA1c= Glycated haemoglobin; HR=hazard ratio; HT=hypertension; HF=heart failure; IHD= ischemic heart disease; MCE=major coronary event; MI=myocardial infarction; MPR= medication possession ratio; NA=not available; OR=odds ratio; PAD=peripheral arterial disease; PDC=proportion of days covered; Ref= reference; RR=relative risk; TC=total cholesterol.

2.2.4 Confounding in pharmacoepidemiological statin studies

In comparison with RCTs, observational studies on intended and beneficial statin effectiveness face different challenges because of the strong confounding by indication (Danaei *et al.* 2012, Smeeth *et al.* 2009, Seeger *et al*. 2003). Confounding by indication arises from the fact that those taking the drug differ from those not taking the drug with respect to their underlying medical indication (Rothman 2002). It is noteworthy, that confounding by indication may arise even in situations where the comparison groups include only patients with the same medical indication, since patients taking different medications to treat their disease will typically have differences in disease severity or other risk factors (Rothman 2002). When there are systematic differences between a group of patients exposed to the study intervention versus the chosen comparator group, it may give rise to confounding of any sort (Brookhart *et al.* 2010). As a result, the effect of the exposure on the outcome is mixed with the effect of another variable, the confounder (Rothman 2002, Vandenbroucke *et al.* 2007).

By definition, a confounding variable is associated with both the exposure and the outcome without being an intermediate variable on the causal pathway from exposure to outcome or any other effect of the exposure (Rothman 2002). For comparison, when one factor modifies the association between another factor and the outcome and, hence, the effect differs between strata, the situation is called an effect measure modification or interaction (Rothman 2002, Rothman and Mahon 2004, Vandenbroucke *et al.* 2007).

In the controlled clinical trials, a successful randomisation procedure eliminates the effect of confounding (Schneeweiss 2006). In real-world, physicians exercise clinical judgement about the necessity for initiating a pharmacological treatment based on the individual patient´s perceived risk for outcome in relation to the modifiable risk factors present. In other words, a random allocation of exposure is not desirable or even feasible in everyday clinical care, which may give rise to confounding in pharmacoepidemiological studies using real-world data. Therefore, these studies have used several strategies to control for the measured and unmeasured confounding (Figure 2.3).

With regard to measurable differences, standard statistical approaches, such as multivariable outcome models and propensity score methods, can be used to control for the confounding effects (Brookhart *et al.* 2010, Schneeweiss 2006). However, the application of statistical approaches requires that the confounding factors can be reliably measured, and that their effects on the exposure or outcome are correctly modelled (Brookhart *et al.* 2010). Additionally, administrative database studies frequently miss detailed information on clinical parameters and prognostic variables that are likely to guide the choice of treatment initiation in clinical practice. This may result in unmeasured differences between the comparator groups and the possibility for residual confounding (Brookhart *et al.* 2010, Schneeweiss 2006). At the meta-analysis level, the HR for mortality among patients with prior CVD and using statins in clinical practice was observed to be reduced by as much as 50% compared to patients not using statins (Danaei *et al.* 2012). Even if the analysis was restricted to patients initiating

statins, the HR for mortality was 0.77 in clinical practice, lower than the HR for mortality of 0.84 observed in the controlled statin trials (Danaei *et al.* 2012). The authors discussed this discrepancy between clinical practice and the RCTs and considered that it might be attributable to the presence of residual confounding (Danaei *et al.* 2012). Therefore, while taking measurable confounders into account is crucial in pharmacoepidemiological statin studies, this should not be assumed to establish causality but merely an association between the statin exposure and outcome under study (Vandenbroucke *et al.* 2007).

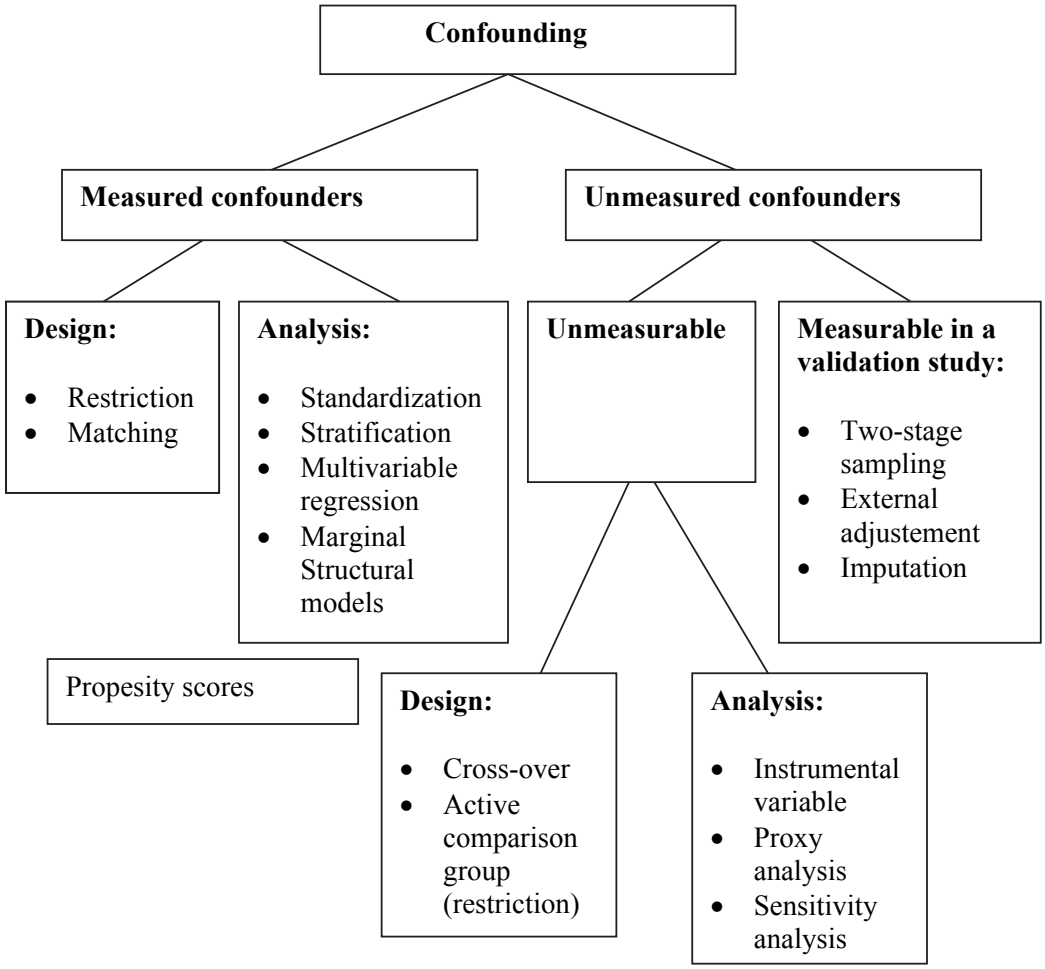

Figure 2.3. Description of selected strategies to control for confounding in pharmacoepidemiological studies (based on Schneeweiss 2006, Glynn *et al.* 2006, Rubin 2007, Brookhart *et al.* 2010, Robins *et al.* 2000 and Schneeweiss *et al.* 2012).

3 AIMS OF THE STUDY

The purpose of this study was to evaluate the trends, patterns and effectiveness of statin use in everyday life. The specific aims were:

1. To describe nationwide secular trends in the incidence and prevalence of statin use in Finland with special emphasis placed on patient groups underrepresented in the randomised, controlled statin trials, i.e. the elderly patients and women.

2. To evaluate the representativeness of two landmark statin trials in diabetes, the Heart Protection Study and the Collaborative Atorvastatin Diabetes Study, for real world care as evidenced by trial eligibility criteria, statin interventions and participant characteristics including the background risk for CVD events and adherence to statin therapy.

3. To study the association between adherence to statin therapy and the risk of major cardiovascular events among patients with diabetes.

4 MATERIALS AND METHODS

4.1 Data sources

All studies used data from the administrative health databases generated through the universal drug reimbursement and health care systems covering all ~5.4 million residents in Finland.

4.1.1 Prescription Register

The prescription register was introduced in 1994 and is managed by SII (Furu *et al.* 2010). The Register collects data on prescription drug purchases reimbursed at the pharmacy to Finnish residents living in non-institutional settings. For each purchase, the data include the prescribing physician, the dispensing date, the ATC code according to the WHO for the active substance (WHO 2013) as well as the strength and the quantity dispensed. The purchases are linked to each individual by a unique social security number. Over-the-counter medicines are entered into the register only when they are prescribed by a doctor. Patients staying in a public nursing home or hospital without interruption for over 90 days are not eligible for drug reimbursement and, therefore, their purchases are not registered. These patients are identifiable from the SII register. In 2003, 94.6%, the vast majority, of the outpatient consumption for LLDs, primarily for statins, was covered by the Register (Martikainen J, the SII, personal communication). Medicines reimbursed by workplace sickness funds became available in the register since 2007.

4.1.2 Special Refund Entitlement Register

The Special Refund Entitlement Register was introduced in 1964 and is managed by the SII (Furu et al. 2010) The data include information on entitlement to higher rates of reimbursement because of certain severe, chronic conditions, such as CHD, diabetes, pulmonary disorders, rheumatoid arthritis and organ transplantations. The eligibility for special reimbursement is based on predefined criteria, a written certificate by the patient's treating physician, and a review process conducted by the SII (www.kela.fi). In 2005, the proportion of Finnish inhabitants receiving special reimbursement for medication costs was 21% (National Agency for Medicines and The Social Insurance Institution 2006).

4.1.3 Finnish Hospital Discharge Register

The Finnish Hospital Discharge Register (FHDR) was introduced in 1969 and is managed by the National Institute for Health and Welfare. FHDR is a nationwide, individual level hospital discharge register and it is one of the oldest in the world (Sund 2012). It contains detailed clinical and administrative data on hospital admission and discharge such as dates, discharge diagnoses and in-hospital procedures. The data also

include clinical information on outpatient hospital visits (since 1998) and day surgical procedures (since 1994). The register covers all Finnish hospitals. The 10th revision of the International Classification of Diseases (ICD-10) has been in use since 1996. During 1969−1986 diagnoses were recorded according to the ICD-8 and during 1987−1995 according to the ICD-9 revision (Sund 2012). The procedure codes have followed the Finnish version of Nordisk Medicinalstatistisk Komité procedure classification since 1996 whereas the National League of Hospitals classification was followed from 1986 to1996. The validity of the Finnish Hospital Discharge Register for capturing CVD events (including stroke and myocardial infarction) is good. From 1988 to 2002 the sensitivity and positive predictive value of the register have been 82–86% and 85–90%, respectively (Sund 2012).

4.1.4 FinDM database

The Diabetes in Finland (FinDM) database was originally constructed for monitoring diabetes epidemiology, diabetes-related complications, and diabetes care (Sund and Koski 2009). It combines data from the nationwide administrative health registers managed by the SII, the National Institute for Health and Welfare, and Statistics Finland. The register data are linked on an individual level using personal identification codes. The data base collects information on all reimbursed prescription drug purchases, entitlements for special reimbursements, all inpatient care in hospitals and primary care wards, day surgical procedures and outpatient hospital visits with diagnostic information and admission and discharge dates. In addition, the dates and causes of death are available (since 1971). The validity of the database for covering patients with pharmacologically treated diabetes in clinical practice in Finland is good in general (Sund *et al.* 2010). However, the database does not have information on patients, who are on diet therapy only and have not required any hospital care due to diabetes.

4.2 Study populations

The study populations included in the individual studies are described in Table 4.1.

Study I identified all persons purchasing reimbursed prescriptions for LLDs between the years 1995 and 2005 in Finland. The subjects were further categorized as incident or prevalent users of LLDs for each study year. The prevalent users in a study year were persons who redeemed at least one reimbursed LLD prescription during the respective calendar year. By definition, prevalent users included both those already using LLDs at the beginning of the study year and those categorised as incident users, i.e. new users initiating their LLD use at any given time during the respective year (Hallas 2005).The count for incident, new LLD users warranted a definition for the the length of the period with no records on LLD use preceding the initiation (Hallas 2005). All study subjects were further stratified by gender and age (those aged 44 years or less, those aged 45–54, 55–64,65–74 years and those aged 75 years or more) of the user.

Table 4.1.Study populations and relevant study characteristics.

	Study I	Study II	Study III	Study IV
Study population	All persons purchasing reimbursed prescriptions for LLDs	Patients with diabetes* initiating statin use	Patients with a special reimbursement for diabetes initiating statin use	Patients with a special reimbursement for diabetes initiating statin use
Study period	1.1.1995-31.12.2005	1.1.2005-31.12.2008	1.1.1995-31.12.2007	1.1.1995-31.12.2006
Period without statin purchases (see text)	1 year	3 years for all	≥ 1 year	≥ 1 year
Data sources	Prescription Register	FinDM database	Prescription Register Special Refund Entitlement Register Finnish Hospital Discharge Register	Prescription Register Special Refund Entitlement Register Finnish Hospital Discharge Register
Exposure of interest	**Statins:** Simvastatin Lovastatin Pravastatin Fluvastatin Atorvastatin Cerivastatin Rosuvastatin **Fibrates:** Clofibrate Bezafibrate Gemfibrozil Fenofibrate **Other LLDs:** Cholestyramine Colestipol Ezetimibe	**Statins:** Simvastatin Lovastatin Pravastatin Fluvastatin Atorvastatin Rosuvastatin	**Statins:** Simvastatin Lovastatin Pravastatin Fluvastatin Atorvastatin Cerivastatin Rosuvastatin	**Statins:** Simvastatin Lovastatin Pravastatin Fluvastatin Atorvastatin Cerivastatin Rosuvastatin

*As defined by the register data. Abbreviations: LLD=lipid lowering drug.

The patients with a special reimbursement for diabetes who initiated statin use (Study III and IV) were those deemed eligible for a special reimbursement for medication costs due to diabetes of any type. The patients with diabetes of any type and initiating statin use (Study II) were either reimbursed for purchases of drugs used in the treatment of diabetes (ATC code A10) or were eligible for special reimbursement for medication costs due to diabetes or had a primary or secondary hospital discharge diagnosis for diabetes. The length of the period without any records on statin purchases that was used for defining incident use,varied between the studies (Table 4.1) while the prescription data in 1994 were used to ensure at least a one-year period without statin purchases for all.

4.3 Study designs

Studies I and II described the relevant characteristics of patients initiating statin use. Furthermore in Study II, real-world patients with diabetes initiating statins were categorized into those eligible or ineligible according to the eligibility criteria applied in the subanalysis of the HPS trial on patients with diabetes, i.e. the HPS (DM) trial and the CARDS trial (table 4.2) with also cumulative outcome data stratified accordingly.

Studies III and IV were case-control studies nested within a cohort of patients with diabetes and initiating statin use. In studies III and IV, patients experiencing a CVD event during follow-up were considered as cases. In the selection of the controls, incidence density sampling was used within the nested case-control design. This involved matching each case to a sample of patients at risk of the event at the time of case occurrence and resulted in an equally long follow-up period available for the cases and their controls. This permitted subsequent calculation of adherence to statins during follow-up for both cases and controls.

Table 4.2. A selection of the most relevant trial eligibility criteria applied in the HPS-DM (Collins *et al.* 2003) and CARDS (Colhoun *et al.* 2004) trials.

	HPS-DM	CARDS
Inclusion criteria	Age 40–80 years, non-fasting blood TC concentrations of ≥3·5 mmol/L and a medical history of: (1) CHD (i.e. MI, unstable or stable AP, coronary artery bypass graft, or angioplasty) or (2) occlusive disease of non-coronary arteries (i.e. non-disabling stroke not thought to be haemorrhagic, transient cerebral ischaemia, leg artery stenosis (e.g. intermittent claudication), carotid endarterectomy, other arterial surgery, or angioplasty) or (3) DM or (4) treated HT (for males aged ≥ 65 years), as applied in the original HPS trial (Heart Protection Study Collaborative Group2002)	Age 40–75 years and type 2 DM of non-secondary origin and diagnosed ≥ 6 months prior to study entry, low LDL cholesterol (≤4·14 mmol/L), serum triglycerides (≤6·78 mmol/L), and at least one of the following: (1) a history of HT, (2) retinopathy (i.e., any retinopathy, maculopathy, or previous photocoagulation), (3) microalbuminuria or macroalbuminuria, defined as a positive Micral or other strip test, an albumin creatinine ratio of 2·5 mg/mmol or greater, or an albumin excretion rate of 20 µg/min or more on timed collection or (4) current smoking with no minimum number of cigarettes per day required.
Exclusion criteria	A clear indication for statin therapy as judged by the participants' treating physicians, a MI, stroke or hospital admission for AP within the previous 6 months, a chronic liver disease (cirrhosis or hepatitis) or abnormal liver function (e.g. alanine aminotransferase level of >67 IU/L), severe renal disease, or impaired renal function (creatinine >200 µmol/L), inflammatory muscle disease or evidence of muscle problems (creatine kinase >750 IU/L), concurrent treatment with ciclosporin, fibrates, or high-dose niacin, child-bearing potential, severe heart failure, a life-threatening disease other than vascular disease or diabetes (e.g. severe chronic airways disease or any cancer other than non-melanoma skin cancer), conditions that could limit long-term compliance (e.g. severely disabling stroke, dementia, or psychiatric disorder).	Prior MI, AP, coronary vascular surgery, cerebrovascular accident, or severe peripheral vascular disease (defined as warranting surgery), uncontrolled hypertension, a plasma creatinine concentration of >150 µmol/L, HbA1c level of >12%, active liver disease or hepatic dysfunction or <80% compliance with placebo (during the run-in period).

Abbreviations: AP= Angina pectoris; CHD= Coronary heart disease; DM= diabetes mellitus; HbA1c= glycated haemoglobin; HT= hypertension; LDL= low density lipoprotein; MI= myocardial infarction ;TC= total cholesterol

4.4 Adherence to statin use

Adherence to statin use was investigated in Studies II-IV. In study II, the adherence to statin therapy was deemed as a relevant characteristic in evaluating the representativeness of the reviewed statin trials for real-world patient care. Adherence was calculated for all cohort members as the truncated MPR (Leslie *et al.* 2009). On the other hand, adherence in studies III and IV was calculated for all cases and their controls as the PDC (Andrade *et al.* 2006). In both calculations, the total number of statin tablets dispensed during the follow-up was divided by the total number of days of follow-up. The difference in nomenclature arises from the differences in the statistical analysis: both are continuous measures, of which PDC better accounts for overlapping prescriptions (Leslie *et al.* 2009).

While the Prescription Register does not cover information on prescribed daily doses, the adherence calculations were based on the assumption of one statin tablet per day being prescribed during the study period. This was considered reasonable since physicians prefer simple drug regimes and the reported prevalence of prescribed daily dosages other than 1 tablet or capsule per day has been a mere 1-4% (Dormuth *et al.* 2007, Lesen *et al.* 2011, Romppainen *et al.* 2014). Good adherence to statin use was defined with a conventional cut-off value at MPR or PDC ≥80% (Benner *et al.* 2002, Schneeweiss *et al.* 2007, Perreault *et al.* 2009a, Perreault *et al.* 2009b).

In an attempt to furher investigate the clinical impact of varying adherence to the cumulative statin exposure in study II, the daily statin doses both at initiation of statin therapy and at the end of a 1- year of follow-up were calculated for patients surviving for 365 days after the statin initiation and with at least one refill during the latter part of the follow-up year (i.e. between 180 and 365 days after initiation).

4.5 Cardiovascular outcomes

All studies with outcome data available (Studies II-IV) focused on the occurrence of hard CVD events. In Study II, a composite endpoint of hard CVD events was chosen as the outcome of interest, analogously to the outcomes studied in the reviewed HPS (DM) and CARDS trials. The composite end point included acute MI (as a primary or secondary discharge diagnosis of ICD-10 I21, I22) and/or a coronary revascularisation procedure (procedure codes for coronary artery bypass grafting, angioplasty, or stenting), stroke (as a primary or secondary discharge diagnosis of ICD-10 I60, I61, I63), or CVD given as a primary cause of death (ICD-10 codes I20–I25, I46, R96, R98, G45, and I60–I69) according to Winell *et al.* (2010). In study II, the risk of CVD events during statin therapy was considered to reflect both the patient's background risk for CVD events and the effectiveness of statins in reducing CVD, as previously proposed by van Staa and colleagues (van Staa *et al.* 2013). Statin therapy was found to reduce the relative risk of CVD events by 22% in the HPS (DM) trial (Collins *et al.* 2003) and by 37% in the CARDS trial (Colhoun *et al.* 2004). If a corresponding treatment effect among the real-world cohort of patients with diabetes initiating statin use was assumed, the underlying CVD risks in the absence of statin treatment would

translate to CVD event rates 22% to 37% higher than those actually observed in the real-world.

Major coronary events (MCEs) and ischemic stroke were evaluated as the outcomes of interest, separately in studies III and IV. The cases in Study III were defined as patients who experienced a composite of MCEs after first surviving at least nine months since statin initiation. The composite MCE included hospitalization for an acute MI (as a primary or secondary discharge diagnosis of ICD-10 I21, I22, or ICD-9 410.x) and/or for coronary revascularization (procedure codes for coronary artery bypass grafting, angioplasty or stenting. The cases in Study IV were defined as patients experiencing an ischemic stroke (ICD-10 code I63 as the primary or secondary discharge diagnosis) after surviving for at least 1 year since statin initiation. An exclusion of the first months of follow-up in both studies (9 months in Study III and 12 months in study IV) was selected because of the lag time reported for statin efficacy in preventing CVD events (Collins *et al.* 2004, Baigent *et al.* 2005, Law *et al.* 2003), to allow for stable computation of adherence and to avoid protopathic bias (Korhonen *et al.* 2009) occurring when the pharmaceutical agent under study is prescribed for an early manifestation of the studied disease (the study outcome) that has not yet been diagnostically detected (Horwitz and Feinstein 1980).

4.6 Control for confounding

In the nested case-control studies (III, IV), several strategies were used to control for measured and unmeasured confounding (Table 4.3). Two separate main analyses were conducted according to the patient´s CHD status at statin initiation in Study III. Patients with a hospital discharge diagnosis of MI, angina or data captured on a coronary revascularization procedure within the previous 7–year period as well as those having ever been eligible for special reimbursement for CHD were included within the group of patients with prior CHD. Patients not covered by any of these criteria were considered as being members of the group of patients without prior CHD.

Another approach to control for measured confounding was used in Study IV where a large variety of potential confounders were accounted for in a secondary analysis using the inverse probability of treatment weighing (Platt *et al.* 2012). This represents the propensity for good versus poor adherence to statins over the whole follow-up period as predicted for all cases and their randomly selected controls based on all measured variables at statin initiation.

Additionally, in an attempt to explore the impact of unmeasured confounding, additional analyses were conducted in both studies (Table 4.3). To investigate the impact of health-seeking behaviour (Brookhart *et al.* 2007, Dormuth *et al.* 2009) on the findings from Study III, external data from the Health 2000 Health Examination Survey was used. This data had been gathered from a nationwide cross-sectional survey carried out in Finland in 2000–2001 and covered various clinical and lifestyle variables not generally available in administrative registries (Aromaa *et al.*

2002). Of the 8028 persons included in the survey, 854 statin users were identified including individuals both with and without diabetes. Furthermore, a sensitivity analysis with the rule-out approach (Schneeweiss *et al.* 2006) was conducted in both studies to assess how strong an association between an unmeasured confounder and adherence, and the confounder and outcome would have solely explained the study findings.

Table 4.3. Description of strategies used to control for confounding (Studies III and IV).

Design	**Study III**	**Study IV**
Restriction	To patients with diabetes aged 45 to 75 years at statin initiation. To patients with no history of organ transplantation according to the Special Refund Entitlement Register at statin initiation.	To patients with diabetes aged 45 to 75years at statin initiation. To patients with no history of organ transplantation according to the Special Refund Entitlement Register at statin initiation.
Matching	Cases and controls were matched according to gender and time of cohort entry (+/-60 days)	Cases and controls were matched according to the year of birth (+/-1 year), gender and time of cohort entry (+/-60 days)
Analysis		
Stratification	Analysis stratified according to CHD status at statin initiation (see text).	Not applicable.
Multivariable regression	Conditional logistic regression analysis. For variables included in the analysis see table 4.4.	Conditional logistic regression analysis. For variables included in the analysis see table 4.4. A secondary analysis with inverse probability of treatment weighting (see text).
Additional analyses		
Unmeasured confounding	A sensitivity analysis with the rule-out approach (see text in section 4.5). An explorative analysis with external survey data (see text in section 4.5).	A sensitivity analysis with the rule-out approach (see text in section 4.5).

Abbreviations: CHD= coronary heart disease.

4.7 Statistical analyses

In Study I, the 1 year period prevalence of statin use was identified from the number of persons deemed to be prevalent statin users during the respective study year divided by the number of inhabitants in Finland (as given by the SII) at the end of the calendar year. Similarly, the 1 year incidence of statin use was calculated from the number of persons deemed as incident users during the respective year divided by the number of inhabitants in the respective year. Persons with at least one statin prescription during the previous year were excluded from this count. Both prevalence and incidence were calculated for the various age groups and separately for both genders. Finally, the Poisson regression was used to calculate the rate ratios and their 95% confidence intervals for each 1-year prevalence and incidence in relation to the reference year 1995.

Descriptive statistics were used in Study II to determine the proportions of real-world patients meeting all the eligibility criteria applied in the HPS (DM) and CARDS trials. Furthermore, the proportions of those meeting any single criteria for trial exclusion were determined regarding both trials. Subsequently, the cumulative hazard functions for the composite endpoint of CVD events were calculated for the identified groups along with a stratified survival analysis. The overall MPR and the proportions of real-world patients surviving each year of follow-up with MPR $\geq$ 80% were also determined using descriptive statistics as were the other patient characteristics deemed relevant for trial representativeness.

Descriptive statistics were also used in Studies III and IV to characterize the cases and their controls. A conditional logistic regression analysis was used to estimate the odds ratios (OR) (Study III) or rate ratios (RR) (Study IV) and their 95% confidence intervals (CI) for the selected CVD events associated with good adherence to statin use. Because the incidence density sampling was used for selecting controls at the time of case occurence, the OR can be considered as an approximation of the RR for the outcome (Opatrny *et al.* 2008). Thus, RR is used subsequently in this thesis to describe both relative outcome measures.

The multivariable models in Studies III and IV were conditional on the matching factors (table 4.3). The variables included in the final models in Study III (table 4.4) were selected based on their potential to act as confounding factors. Therefore, the presence of familial hypercholesterolemia and pulmonary disorders (asthma or chronic obstructive pulmonary disease, as identified from the Special Refund Entitlement Register), use of thiazolidinediones, clopidogrel, spironolactone and antidepressants, and socioeconomic status (as a nine-category variable according to employment and occupation) were not included in the final models as they did not affect the ORs for the main exposure (change <2%) when added to the final models. The multivariate model in Study IV included all measured variables. Additionally in Study III, the potential of prior CHD at statin initiation to act as an effect modifier was studied using pooled data from both risk groups.

Table 4.4 Description of variables included in the final multivariable analyses (Studies III and IV).

	Measured variables in Study IV	**Measured variables in Study III**
Age, years	-(see text)	X*
Duration of diabetes, years	X	X*
Duration of CHD, years (categorical)[1]	-	X
Medical characteristics at cohort entry		
Cerebrovascular disease or PAD	-	X
History of any atherosclerotic CVD (cerebrovascular disease, CHD [chronic or acute], peripheral arterial disease)	X	-
Congestive heart failure	X	X
Arrhythmias	X	-
Microangiopathic complications (retinopathy, neuropathy, nephropathy or dialysis)	X[2]	X[3]
Moderate to severe hypertension	X	X[4]
Rheumatoid arthritis	X[2]	X[4]
pulmonary disorders (asthma or chronic obstructive pulmonary disease)	X[2]	-(see text in section 4.6)
Depression	X[2]	-
Psychosis	X[2]	-
Cancer	X[2]	-
Epilepsy	X[2]	-
Alcohol-related disease	X[2]	-
Sleep apnea	X[2]	-
Socioeconomic status	X	-(see text in section 4.6)
Region of residence (hospital district)	X	-

Table 4.4 Description of variables included in the final multivariable analyses (Studies III and IV) *(Continued)*.

	Measured variables in Study IV	Measured variables in Study III
Medication use		
Antidiabetic medication		
Only oral blood glucose lowering drugs: (biguanides, sulphonylureas, thiazolidinediones, guar gum, repaglinide and/or nateglinide)	X	X
Only insulin	X	X
Both oral and insulin	X	X
No antidiabetic drug therapy	X	X
Concomitant medications		X
Fibrates		
Warfarin	X	X
Platelet inhibitors	X	-(see text in section 4.6)
Spironolactone	-	-(see text in section 4.6)
Antidepressives	X	-(see text in section 4.6)
Hormone replacement therapy	X	X
Antihypertensive medication (diuretics, beta-adrenergic antagonists,calcium channel blockers, ACE inhibitors or angiotensin receptor blockers)	X	X
Number of cardiovascular drugs[5]	-	X
Digitalis glycosides	X	-
Nitrates	X	-
Dispensing delay (the time between the first prescription of a statin and the first dispensing)	X	-

All variables were measured at statin initiation unless otherwise stated. Data for medication use was measured from the preceding 365 days and for medical characteristics either as applicable ICD-codes from the preceding 7 years and/or as entitlement for special reimbursement, unless otherwise stated. [*]Measured at the date of event occurrence for cases and their controls, treated as continuous variables for patients without prior CHD and as categorical variables for patients with prior CHD at cohort entry. [1]For patients with prior CHD at cohort entry. [2]Based on hospitalizations during the previous 365 days and/or entitlements for special reimbursement and/or applicable drug purchases. [3]Based on applicable ICD codes. [4]Based on entitlement for special reimbursement. [5]Based on the use of antithrombotic therapy, digitalis glycosides/antiarrhythmic drugs/nitrates, miscellaneous antihypertensive drugs, diuretics, pentoxifylline, beta-adrenergic antagonists, calcium channel blockers and ACEinhibitors/ angiotensin receptor blockers. Abbreviations: CHD= coronary heart disease; CVD= cardiovascular disease; PAD= peripheral arterial disease.

To further analyse the possibility for a dose response between increasing level of adherence to statin use and the incidence of subsequent CVD events, adherence in both studies was defined as a continuous variable and further as a three-category variable (PDC <40%, 40–79% or ≥ 80%, Study III) or as a five-category variable (PDC <20%, 20%–39%, 40%–59% 60%–79% or ≥80%, Study IV). Additionally, the type and dose of a statin at initiation were captured in both studies and categorized into different intensity groups. All studies in this thesis used somewhat differing definitions on statin intensity since simvastatin equivalent doses reflecting the available evidence at the time the study was conducted (Law *et al*. 2003, U.S. Food and Drug Administration 2012, Stone *et al.* 2014). In study III, the intensity of initiating statin was used only for describing the characteristics of both cases and their controls and only of controls (relecting the source population) and dichotomized according to the level of adherence to statin use. In study IV, the information on the intensity of the initiating statin was combined with that on adherence level in order to create four statin exposure groups; moderate intensity (e.g. simvastatin 20–80 mg) with good adherence, moderate intensity with poor adherence, low intensity (e.g. simvastatin < 20mg) with good adherence and low intensity with poor adherence. The number of patients initiating with high intensity statin (atorvastatin ≥40mg, rosuvastatin ≥ 20mg) was so small that they were excluded from these exposure groups.

All analyses were conducted with SAS software (version 9.1 or 9.2; SAS Institute, Inc., Cary, NC, USA).

4.8 Approvals and ethical considerations

The protocols for the Studies III and IV were approved by the SII, the National Data Protection Agency and the National Institute for Health and Welfare, Helsinki, Finland. The protocol for Study I was approved by the SII as part of a larger research project.

Data management in Study I and data linkages in studies III and IV were performed by the SII. In all of these studies, the investigators received either unidentifiable patient data (Studies II-IV) or statistics (Study I). In none of the studies were patients contacted. Thus, there was no legal requirement to obtain ethics committee approval. However, Study II was approved by the ethics committee of the National Institute for Health and Welfare, Finland, as part of a larger diabetes research project. Data management and data linkage in Study II were performed by the National Institute for Health and Welfare and additional permissions to collect data from the FinDM database were obtained from the maintainers of the registers.

5 RESULTS

5.1 Trends in statin use in Finland from 1995 to 2005 (Study I)

A total of 603 866 persons had received at least one prescription for a LLD in Finland from 1995 to 2005. The vast majority, 98%, received at least one prescription for a statin and thus the study focused on statin use. The proportion of the whole Finnish population with statin use increased from 0.8% to 8.9% during the study years.

Among females, the prevalence increased from 6.9 per 1000 female inhabitants to 89.3, and in males from 8.8 to 88.5 per 1000 male inhabitants from 1995 to 2005. From 1995 to 1999, the prevalence of statin use was statistically significantly higher in males than in females but in 2002 the situation reversed and for the rest of the study period, the prevalence was higher in females (p-value <0.05 for a statistically significant difference between the genders).

In 1995, the 1 year incidence was higher in males than females (RR 1.3, 95% CI 1.2, 1.3) but since 1996 no significant difference was observed. Persons aged between 65 and 74 years showed the highest incidence in both genders over the whole study period (Figures 5.1 a and b). The relative increase in incidence from 1995 to 2005 was the highest in persons aged at least 75 years (RR 14.0, 95% CI 12.5, 15.7 for males and RR 14.1, 95% CI 13.0, 15.3 for females).

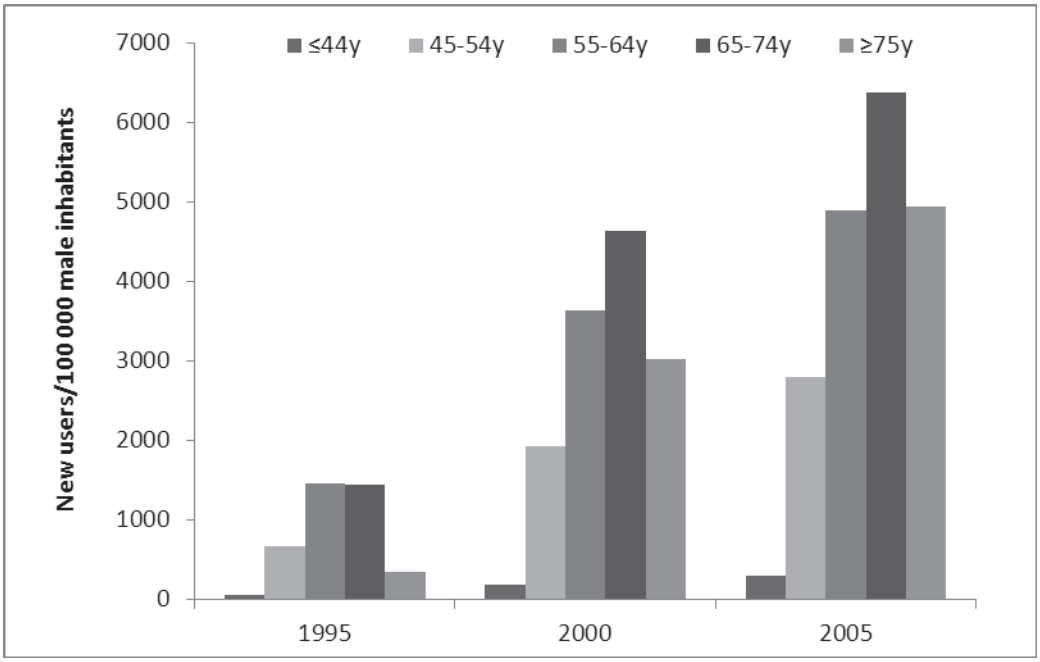

Figure 5.1 a The 1-year incidence of statin use among males in Finland during the years 1995, 2000 and 2005.

5.2 Representativeness of the Heart Protection Study and the Collaborative Atorvastatin Diabetes Study of real-world diabetes care (Study II)

A total of 56 963 patients with diabetes initiated statin use between 2005 and 2008 in Finland. Most of them, 73% (N=41 552), had no apparent CVD (defined as myocardial infarction, AP, unstable AP, stroke, transient ischaemic attack or peripheral vascular disease, surgical procedure codes for coronary revascularisation, amputation or other peripheral vascular procedure for atherosclerosis or special reimbursement for CHD) at cohort entry. Fifty seven per cent of the patients were deemed to meet all the eligibility criteria of the HPS (DM) trial: The most common reasons for not meeting the eligibility criteria were age less than 40 or more than 80 years (10% of all initiators), a recent CVD event, including MI, stroke, or hospital admission for angina pectoris, within the previous 6 months (10%) or the presence of a life-threatening condition other than vascular disease, e.g. cancer, asthma or chronic obstructive pulmonary disease (20%).

With respect to the patients with no established CVD, 49% met the criteria for the CARDS trial, while the most common reasons for not meeting the eligibility criteria were age less than 40 or more than 75 years (15% of all initiators without CVD), diabetes diagnosed during the previous 6 months (14%) or no previous records on hypertension, retinopathy or micro/macroalbuminuria (28%). In summary, patients with a recent CVD event (within ≤ 6 months before statin initiation) were deemed ineligible for both trials.

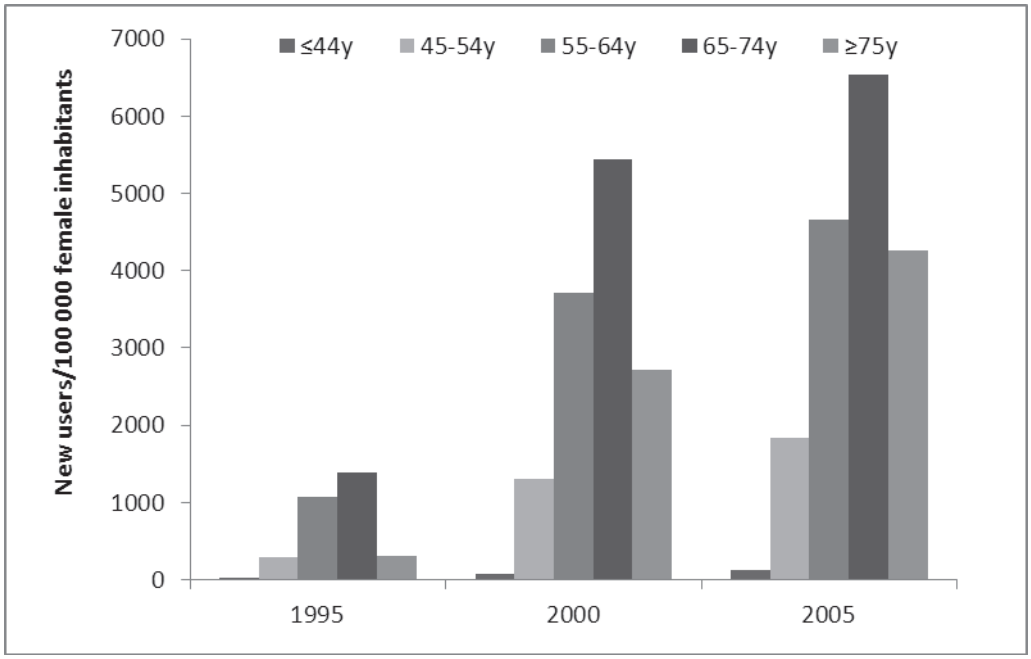

Figure 5.1 b The 1-year incidence of statin use among females in Finland during the years 1995, 2000 and 2005.

With respect to the patients with diabetes and initiating statins, 8 714 patients (15%) encountered a major CVD event during a mean follow-up of 3.4 years. In the patients deemed ineligible for the HPS (DM) trial, the cumulative risk for a CVD event was two to three times that of those deemed eligible. In the patients deemed ineligible for CARDS, the cumulative risk was of the same magnitude among those deemed either eligible or ineligible for the trial. With respect to the representativeness of the background risk for CVD events among the participants in the reviewed trials for real-world patients, the CVD event rate observed in the HPS (DM) trial, about 20% in the placebo arm over 4 years (Collins *et al.* 2003) was found to approximate to the event rates observed in the study for all real-world patients with diabetes (about 15% in 4 years), irrespective of trial eligibility. Correspondingly, the CVD event rate observed in CARDS, which was about 10% in the placebo arm in 4 years (Colhoun *et al.* 2004), was found to approximate the event rates observed in the study for all real-world patients with diabetes and without CVD (about 9 % in 4 years).

Compared with both trial populations, there were less men among the real-world patients (Table 5.1). The proportion of patients with CVD (or CHD) was lower (27% vs. 51%) in the real-world as compared to the HPS (DM) trial and the mean duration of diabetes was shorter (7.6 vs. 9.3 years). As compared to the CARDS trial, the mean duration of diabetes seemed well balanced between the real-world patients and the trial participants but considering that newly diagnosed diabetes was an exclusion criterion in CARDS, 14% of the real-world patients were categorized as newly diagnosed. The use of various antihypertensive medications and metformin was more common in the real-world as compared to both trials, and the use of sulphonylureas was less common (Table 5.1).

With respect to the real-world patients surviving the first year after statin initiation, one quarter (27%) of all and 29% of those without CVD had a statin initially prescribed at a dose corresponding to <20 mg of simvastatin. The majority (52–54%) of patients initiated statin use with a dose corresponding to 20 mg of simvastatin and 5% with a high dose statin corresponding to ≥ 80mg of simvastatin (Figure 5.2). After the 1-year follow-up, there were no relevant changes observed in the corresponding proportions (Figure 5.2).

Table 5.1 Characteristics of the real-world patients with diabetes initiating statin therapy and of the participants of the HPS-DM (Collins *et al.* 2003) and CARDS (Colhoun *et al.* 2004) trials.

Study population	HPS-DM	Real-world patients with diabetes (all)	CARDS (See footnote)	Real-world patients with diabetes and without CVD[a]
Years of recruitment or cohort entry	1994–1997	2005–2008	1997–2001	2005–2008
Number of patients	5963	56 963	2838	41 552
Mean age in years (SD)	62.1 (8.9)	61.9 (12.4)	61.5 (8.3)	59.5 (12.0)
Men, N (%)	4147 (70)	31 912 (56)	972 (68)	22 605 (54)
Cardiovascular disease, N (%)	3051 (51)	15 411 (27)	0[b]	0
Diabetes duration in years (SD)	9.3 (8.9)[c]	7.6 (8.5)	7.9 (6.4)	7.1 (8.2)
Diabetes duration ≤ 0.5 years, N (%)	NA	7514 (13)	0[b]	5638 (14)
Diabetes treatment, N (%)				
Insulin	NA (25[b])	15 564 (27)	282 (20)	10 874 (26)
Metformin	NA (31)	34 606 (61)	672 (47)	26 716 (64)
Antihypertensive drugs, N (%):				
Beta blockers	NA	23 898 (42)	219 (15)	13 248 (32)
Calcium antagonists	NA	13 686 (24)	304 (21)	8967 (22)
Angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists	NA	32 683 (57)	637 (45)	22 557 (54)
Diuretics	NA	11 942 (21)	262 (18)	6616 (16)

For the CARDS trial only data for the arm treated with statins (N=1428) are presented. NA=data not available. [a]According to previous cardiovascular disease (CVD) status at baseline. [b]Assumed on the basis of trial eligibility criteria.[c]Data for patients with type 2 diabetes.

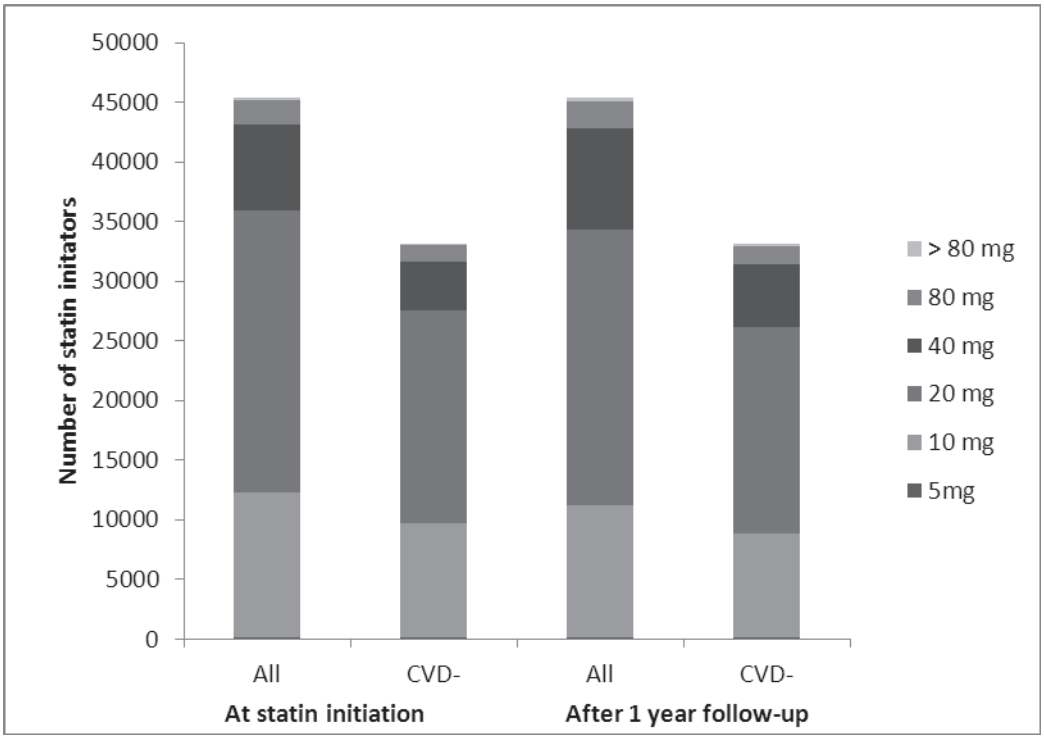

Figure 5.2. Distributions of statin doses as simvastatin equivalents at initiation and after 1 year of follow-up according to the prescriptions redeemed by all patients with diabetes and by those without cardiovascular disease in 2005–2008. For equivalence atorvastatin 10mg = fluvastatin 80mg = lovastatin 40mg = pravastatin 40mg = simvastatin 20mg ≤rosuvastatin 5mg (U.S. Food and Drug Administration 2012).

In the real-world patients, the mean MPR was 72% for a mean follow-up of 3.4 years. For all the years of follow-up, MPRs were less than those reported for the HPS and CARDS trials (table 5.2).

Table 5.2 The proportions (%) of patients with diabetes adherent (MPR ≥ 80%) to study treatment (RCTs) or statin treatment and surviving each study year.

Year of follow-up	HPS†	CARDS*	Real-world diabetic patients initiating statins in 2005 to 2008 (all)*
1	89	90	63
2	85	87	42
3	84	86	40
4	83	78	40
5	82	-	42
Average	85	85	57

*Analysis restricted to surviving patients. †Data available only for the original study population.

5.3 Association between good adherence to statins and the incidence of major cardiovascular events in patients with diabetes (Studies III and IV)

A total of 60 677 statin initiators with diabetes met the eligibility criteria for the study where the outcome was defined as a MCE (i.e. acute MI and/or coronary revascularization procedure). Of these, 6466 (11%) experienced an MCE and 3513 further qualified as cases in the main analyses (Table 5.3). Half of the cases experienced a myocardial infarction: 49 % in those without prior CHD and 52% in those with CHD. The mean follow-up time was 3.7 years for those without prior CHD and 3.2 years for those with a prior CHD at statin initiation. The maximum duration of follow-up was 12.6 and 12.2 years for the groups, respectively.

For comparison, 52 868 statin initiators with diabetes met the eligibility criteria for the study where the outcome was defined as ischemic stroke. Of these, 2517 (4.8%) experienced an ischemic stroke during the mean follow-up of 4.27 years (maximum 12.99 years). A total of 1703 of the cases had at least 1 year of follow-up available in the registries and were included in the main analyses (Table 5.3).

Compared to their matched controls, the cases in these studies tended to have more comorbidities and a longer duration of diabetes. In comparison to all the patients with diabetes initiating statin use in Study II, the patients eligible for special reimbursement for diabetes and identified as controls in these studies more commonly tended to be male and with some kind of antidiabetic pharmacotherapy.

Good adherence to statins (PDC $\geq$ 80%) was associated with a 14% to 16% relative reduction in the incidence of MCEs and a 24% reduction in the incidence of ischemic stroke among patients with diabetes (Table 5.3). With regard to the incidence of MCEs, the association seemed independent of the presence of prior CHD (P = 0.24 for interaction between the study groups, significance level set at <0.2) as for ischemic stroke the association tended to be stronger among those without prior CVD as compared to those with CVD: adjusted RR 0.63 (95% CI 0.52–0.75) versus 0.84 (95% CI 0.69–1.03), P = 0.06 for interaction.

In both studies there was a dose response in terms of an increasing level of adherence to statin use with the subsequent decrease in the incidence of events. For MCEs, the incidence decreased by 3% per each additional 10% unit increase in PDC (adjusted OR 0.97 per 10% units). With respect to ischemic stroke, the incidence decreased by 6% (adjusted OR 0.94 per 10% units). Furthermore, the intensity of the initiating statin had no effect on the incidence of ischemic stroke among those with poor adherence (<80%). However, among those with good adherence, patients initiating with moderate intensity statins seemed to be at a lower risk for having a stroke than those initiating with low intensity statins (reduction in rate ratio 31%, 95% CI 18%–43% vs. 16%, 95% CI 3%–28%, those with poor adherence and initiating with low intensity statins as reference).

Table 5.3. Baseline characteristics of cases and their matched controls at statin initiation with main outcome measures (Studies III, IV).

Study	Year of statin initiation	Number of patients (cases/ controls)	CVD (%)	Age, mean (y)[1]	Male (%)	type 1 DM (%)	Duration of diabetes, mean (y)[1]	HT (%)	TC (mmol/l)[1]	HbA1c (%)[1]	Smoking (%)
III: Patients without prior CHD	1995-2007	2013/15886	NA/NA	64/62*	65/65*	NA/NA	14/12*	73/66*	NA/NA	NA/NA	NA/NA
	Outcome of interest	Incidence of MCEs including hospitalization for an acute MI and/or for coronary revascularization procedure and incidence of MI									
	Outcome measures	MCE: OR 0.86 (95% CI 0.78–0.95) for PDC <80% (ref) vs. PDC≥80% MI: OR 0.82 (95% CI 0.71–0.94) for PDC <80% (ref) vs. PDC≥80%									
III: Patients with prior CHD	1995-2007	1500/4202	100/100	66/65*	69/69*	NA/NA	13/12*	96/95*	NA/NA	NA/NA	NA/NA
	Outcome of interest	Incidence of MCEs including hospitalization for an acute MI and/or for coronary revascularization procedure and incidence of MI									
	Outcome measures	MCE: OR 0.84 (95% CI 0.74–0.95) for PDC <80% (ref) vs. PDC≥80% MI: OR 0.67 (95% CI 0.56–0.81) for PDC <80% (ref) vs. PDC≥80%									
IV	1996-2006	1703/6799	56/38	64/64	63/63	NA/NA	8.4/7.9	NA	NA/NA	NA/NA	NA/NA
	Outcome of interest	Incidence of ischemic stroke									
	Outcome measures	RR 0.76 (95% CI 0.68–0.85) for PDC <80% (ref) vs. PDC≥80%									

*Descriptive statistics for controls weighted by the inverse of the number of controls in the matched set.Abbreviations: CHD= coronary heart disease; CVD= cardiovascular disease; HbA1c= Glycated haemoglobin; HT=hypertension (identified as reimbursed antihypertensive medication); MCE=major coronary event; MI= myocardial infarction; NA=not available; OR=odds ratio; PDC=proportion of days covered; Ref=Reference; TC=total cholesterol

In further secondary analysis employing the IPTW approach, the results in study IV remained essentially the same with an RR for good versus poor adherence of 0.80 (95% CI 0.72–0.89).

The sensitivity analyses evaluating the impact of unmeasured confounders suggested that if the OR between an unmeasured confounder and adherence was <1.5, then ORs of 4 or greater between the confounder and incidence of an MCE would have been required for the ORs observed in the study to be explained completely by confounding. Similarly, if the OR between an unmeasured confounder and adherence was < 2, ORs of 7 or greater between the confounder and incidence of ischemic stroke would have been required for the main OR to be explained completely by confounding.

Among all the statin users identified from the Health 2000 Survey (Aromaa *et al.* 2002), those with good adherence to statins reported less current smoking as compared to those with poor adherence (11% vs. 15%). Similarly, they had less frequently a BMI > 25 kgm^{-2} (63% vs. 71%) and had less frequently elevated blood pressure when this was defined by a cut-off at 140/90 mmHg (47% vs. 57%). In addition, the proportion of women who had participated in screening mammography was higher among those with good adherence to statins (55% vs. 51%). In contrast, leisure-time physical activity was less common among those with good in comparison with those with poor adherence (49% vs. 65%).

6 DISCUSSION

6.1 Trends in statin use in Finland from 1995 to 2005

During a ten year observation period in Finland, there was a substantial increase in both the 1 year prevalence and incidence of statin use. The largest relative increase in incidence was found among those aged 75 years and more and was apparent well before the publication in 2002 of the first statin trials representative for the elderly (Heart Protection Study Collaborative Group 2002, Serreus *et al.* 2002, Shepherd *et al.* 2002). Furthermore, there was also a substantial increase in the incidence and prevalence observed among females despite their underrepresentation in the statin trials. From 1995 to 1999 the prevalence of statin use was statistically significantly higher among males than among females but since 2002, two years prior to the publication of the Finnish Current Care Guidelines which especially emphasised the evidence base for statin therapy for women and the elderly (Dyslipidemia: Current Care Guidelines 2004), the prevalence was already higher in females. Thus, these results suggest that physicians apply clinical trial evidence in clinical decision making going beyond the possible limitations in the representativeness of the RCTs for clinical practice. Nonetheless, the study did not compare the demographic characteristics of those initiating and those not initiating statin use in clinical practice. Hence, there is still the possibility that the under-representativeness of women in the trials has influenced the prescribing patterns and the targeting of statin therapies in clinical practice. In fact, the increase in the proportion of females initiating statin use in Finland in 1995 to 2005 was similar to that described in other European reports from the late 90's and also with a more recent report from the early 21st century from Israel which observed that approximately half of statin initiators were women (Larsen *et al.* 2001, Riahi *et al.* 2001, Shalev *et al.* 2014). However, the recent data from Israel with corresponding data from Finland indicate that women tend to be three to five years older than men at statin initiation (Shalev *et al.* 2014, Rikala *et al.* 2013) and present with higher LDL levels at that time (Shalev *et al.* 2014).

A plateau in the incidence of statin use has occurred from the year 2004 to 2005 in Finland. This was originally interpreted to reflect the decreased coverage of statin purchases in the Prescription Register resulting from the introduction of generic substitution in 2003 with statins being purchased at prices lower than the basic reimbursement level. However, more recent reports from other countries have also revealed a decreasing trend in the overall incidence of statin use since the year 2005 and 2006 (Geleedst-De Vooght *et al.* 2010, Shalev *et al.* 2014) which instead has been interpreted as reflecting the decreasing number of statin-naïve patients at the population level, especially those already suffering from CHD at statin initiation (Shalev *et al.* 2014). This is in agreement with the reports of an increasing proportion of patients presenting with diabetes and without CHD at statin initiation in Finland (Upmeier *et al.* 2013, Rikala *et al*. 2013). This has taken place in parallel with the changes in the Finnish Current Care Guidelines, which have reduced the threshold for statin initiations (after an individually customised risk assessment) to be provided to more patients presenting with diabetes and

without CVD prior to therapy. Simultaneously, a shift in statin use towards the elderly has been reported since 2005 even in countries with declining overall incidences of statin use (Geleedst-De Vooght *et al.* 2010) and also in Finland (Upmeier *et al.* 2013). This may be interpreted as a sign of the overall aging of the population, of successful CVD prevention at lower ages and a shift of CVD morbidity to more advanced ages (Kattainen *et al.* 2006), as well as a sign of an increasing number of statin-naïve elderly patients still presenting without CVD and, perhaps, of less concern about the benefit-risk ratio of initiating statins in patients with a low risk of CVD events at such a late stage of their lives. In any case, the elderly constitute a heterogeneous patient population among whom the decisions to initiate statin therapy should be personalized (Strandberg *et al*. 2014).

6.2 Representativeness of the statin trials of real-world diabetes care

In this study, the selection of a homogenous study population was shown to limit the representativeness of the HPS (DM) and CARDS trials for real-world diabetes care. Only half of the real-world patients with diabetes and initiating statin use would have been deemed eligible for enrollment in these trials. This finding is in line with a previous report on the proportions of real-world patients with atrial fibrillation in the UK considered eligible for participation in the pivotal RCTs of novel oral anticoagulants (48%–64%) (Lee *et al*. 2012) and slightly higher compared to the proportion of patients with type 2 diabetes living in Scotland in 2008 and deemed eligible for the UKPDS conducted more than ten years earlier (32%–51%) (Saunders *et al.* 2013). Increasing the representativeness of RCTs to reflect real-world settings has been emphasised in the new Regulation No 536/2014 of the European Parliament and of the Council on clinical trials of medicinal products for human use. However, there is a trade-off which has to be made. Since a homogenous study population is integral for the internal validity of the trial results (Rothman *et al.* 2013), increasing the representativeness of a trial population for real-world patients may well increase "noise" in the trial population and challenge both the internal validity of the trial results and the power of the trial to show superiority over the comparator. In fact, increasing the representativeness of a statin trial for the real-world setting failed to reveal statin efficacy in preventing all-cause mortality or CHD events when compared to usual care in an unblinded fashion in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT Officers and Coordinators 2002). Nonetheless, as demonstrated here, the representativeness of RCTs can and should be investigated comprehensively with pharmacoepidemiological methods combined with administrative registry data in order to gain more insight into the applicability of the trial findings to the real-world clinical care.

In the real-world patients with diabetes and without CVD, the cumulative risk for major CVD events after statin initiation, reflecting the background risk for CVD events, was similar for those deemed either eligible or ineligible for the CARDS trial. For all real-world patients with diabetes initiating statin use, the cumulative risk for major CVD events was substantially higher among those deemed ineligible as compared to those eligible for the HPS (DM) trial. This reflects both the exclusion of high risk patients with recent CVD events from the HPS (DM) trial and their prevalence among those initiating statin use in routine clinical practice. It is plausible that the totality of evidence for statins

in CVD prevention accumulated since the 1990´s together with the implementation of the Finnish clinical treatment guidelines that have prioritised any pharmacological therapy in dyslipidemia to those individuals with prior CVD, have out-weigthed the possible limitations in the representativeness of individual statin trials in diabetes and as such, guided physicians´ decision making. Furthermore, the background risk for CVD events among all real-world patients with diabetes and without CVD seemed, on average, to be of the same magnitude when compared to participants allocated placebo in the CARDS trial. This was also the case when all patients with diabetes, irrespective of trial eligibility criteria, were evaluated in comparison with the participants in the HPS (DM) trial. Considering that the absolute risk reduction associated with statin therapy in diabetes depends on the background risk for CVD events (Heart Protection Study Collaborative Group 2002, Collins *et al.* 2003, Cholesterol Treatment Trialists' Collaboration 2010), the similarities in the average cumulative risks for CVD events between the more current real-world patients and the trial participants provide an assurance that as a whole, the trial findings can be applied to the relevant real-world patient population.

Furthermore, this thesis describes the representativeness as a two-way street between the trials and the real-world clinical care since it highlights the time-varying nature of representativeness depending on the evolvement of overall treatment practices. Women were under-represented in both HPS (DM) and CARDS, whereas concomitant antihypertensive medications and metformin were more commonly in use in the real-world. HPS (DM) trial also included more participants with prior CVD as compared to patients with diabetes and initiating statin use in the real-world. These limitations in the representativeness of the statin trials merely reflect phenomena which have occurred since the trial recruitment years, i.e. the changes in the diagnostic criteria for diabetes, with statin use now being initiated in the earlier stages of the disease (Dominguez *et al.* 2009, Eliasson *et al.* 2011) accounting also for the high risk of CVD events associated with female gender in diabetes (Kuusisto and Laakso 2013). Metformin is nowadays more commonly used as the first line therapy for type 2 diabetes (Charlton *et al.* 2008, Mann *et al.* 2009), the blood pressure control in diabetes has improved (Charlton *et al.* 2008, Mann *et al.* 2009, Vehko *et al.* 2010) and the mortality in diabetes has declined (Gulliford and Charlton 2009). It is now more rare to find statin-naïve patients with diabetes also presenting with prior CVD at statin initiation compared to the situation during the recruitment years for HPS (DM).

However, as the absolute risk reduction associated with statin therapy depends on the absolute reduction in LDL achieved with statin therapy (Heart Protection Study Collaborative Group 2002, Collins *et al.* 2003, Cholesterol Treatment Trialists' Collaboration 2010), lower adherence to statin use in the real-world as compared to those achieved in the HPS (DM) and CARDS trials seems to be the greatest obstacle to prevent the attainment of the full benefit from statin therapy in clinical practice: Only 15% of participants with diabetes in the RCTs did not adher to their statin therapy while the respective proportion of the real-world patients with diabetes was as much as 40% among those initiating statins in 2005 to 2008. It is also noteworthy that this observation period preceded the year 2010 when statin use was given enhanced and critical media coverage in Finland (http://yle.fi/aihe/artikkeli/2010/11/01/kolesterolipommi), which, in theory, could have further affected adherence. Furthermore, almost 30% of the real-world patients

initiating statin use in 2005 to 2008 were prescribed doses lower than 20mg when expressed as simvastatin equivalents, i.e. doses lower than those used in the HPS (DM) and CARDS (i.e. simvastatin 40mg and atorvastatin 10mg, respectively). The proportion of patients with statin doses lower than those examined in the HPS (DM) and CARDS did not change during a 1-year follow-up confirming the previous claim that up-titration of statin doses up to the evidence based level is rarely conducted in clinical practice (Foley *et al.* 2003, Kiviniemi *et al.* 2011, Simpson *et al.* 2013, Arnold *et al*. 2014).

6.3 Adherence to statin therapy and the incidence of major cardiovascular events in diabetes

The incidence of both MCEs and of ischemic stroke was significantly lower in diabetic patients with good adherence to statin therapy (≥80%) in comparison to those whose adherence was poor. The association between good adherence and the reduction in subsequent CVD events seemed to be stronger for ischemic stroke than for MCEs. Furthermore, the association with MCEs was independent of the background risk for CVD events, the latter defined by the presence of prior CVD events at baseline. With respect to ischemic stroke, the association was stronger among those with a lower background risk for future events.

The causality of the associations observed between good adherence to statin use and the reduction in the incidence of major CVD events may be questioned due to the observational nature of these studies. Studying the intended effects of drugs in clinical practice is prone to strong confounding by indication (Vandenbroucke 2004) possibly distorting the observed associations. Based on the findings from studies III and IV, there were systematic differences between patients with good adherence and those with poor adherence to statin use. Although many measures were undertaken to control for the confounding arising from such differences, the possibility for residual confounding based on both measured and unmeasured variables cannot be excluded. There is evidence suggesting that adjusting for a strong, measured confounder in the multivariate analysis may not suffice as a method to control for measured confounding, especially if the distribution of the variable is highly unbalanced between the exposure groups (Henley *et al.* 2002, Rubin 2007). Furthermore, several unmeasured variables associating with an increased risk for CVD events may also have influenced adherence behavior but, in the light of the evidence, not in any conclusive manner (Mann *et al.* 2010, Latry *et al.* 2011, Lemstra *et al.* 2012, Halava *et al.* 2014). Therefore, the magnitude of the residual confounding in the point estimate for good statin adherence is difficult to determine with certainty.

Nonetheless, based on the criteria for causality proposed by Sir Austin Bradford Hill (Hill 1965) several factors support causality between good adherence to statin use and the decrease in CVD events. First, there was a dose response for the increasing level of adherence and a decreasing incidence of both MCEs and of ischemic stroke. Second, the studies focused on indisputable clinical outcomes occurring after a reasonable duration of follow-up based on which the temporal sequence between exposure and effect could be reliably established. Third, the associations found in these studies for statin adherence and

CVD events were in line with the body of observational evidence analysed at the meta-analysis level (Chowdhury *et al.* 2013). However, comparing the relative risk reduction (RRR) of almost 50% in all-cause mortality associated with good adherence to statin use at the meta-analysis level (Chowdhury *et al.* 2013) with the 22–30% RRR observed at best in the statin RCTs (Scandinavian Simvastatin Survival Study Group 1994, The Long-Term Intervention with Pravastatin in Ischemic Disease Study Group 1998), it seems that also other factors than merely the pharmacodynamic effects of the statins may mediate the influence of good statin adherence on the occurrence of CVD events in clinical practice. However, previous reports from other countries with clinical data on cholesterol levels have indicated that real-world patients with diabetes using statins achieve an absolute reduction in LDL that at its best corresponds to a third of that achieved in the clinical trials (Collins *et al.* 2004, Colhoun *et al.* 2004, Eliasson *et al.* 2011). Furthermore, at least a third of statin treated patients with diabetes do not achieve the target of LDL < 2.5mmol/L (Braga *et al*. 2010). Thus, suboptimal adherence to statin use in clinical practice seems to result in lower cumulative exposure to statins, less pharmacodynamic statin effects being obtained, and less effectiveness conferred by statins in preventing CVD events. This concept is in line with the one already outspoken in the early 20th century by the famous physician, C. Everett Koop, who concluded: "Drugs don´t work in patients who don´t take them".

6.4 Methodological considerations

Due to the reliance on administrative register data, these studies have inherent limitations common to all observational studies utilising a similar approach. The advantages of using administrative register data are the increased speed, limitation of some biases, such as recall and reporting bias, lower cost and the representativeness of routine clinical practice in large populations (Hall *et al.* 2012, Schneeweiss and Avorn 2005). However, the timing of data collection and the detail and accuracy of data are not controlled by the investigator (Hall *et al.* 2012, Schneeweiss and Avorn 2005). Thus, not all drug research questions can be answered with the available, administrative registers. In these situations, therefore, RCTs are warranted (Hall *et al.* 2012).

Incident statin use (Study I) was defined for all new statin users as a one-year period without any record on statin purchases prior to the date of the first statin purchase. As a consequence, the same individual may have appeared as an incident statin user more than once during the study years. Since statin use is dynamic (Korhonen *et al.* 2011) with many middle aged patients initiating statin use and then reinitiating use after long periods of discontinuation at later ages, the amounts of true, statin-naïve initiators among those aged 75 years or more may be smaller than those estimated in the present study.

The proportion of real-world patients with diabetes initiating statin use and deemed eligible for the HPS (DM) and CARDS trails (Study II) may be under-estimated or over-estimated: Some patients with diabetes may not have been captured in the study, especially those aged 65 years or more, with undiagnosed diabetes or on an antidiabetic diet therapy only and not requiring any hospital care (Sund *et al*. 2010). Furthermore, there was no data on laboratory values or smoking behaviour available and some complications such as retinopathy, microalbuminuria and nephropathy, are likely to

have been underreported in the data. Therefore, not all trial eligibility criteria could be defined in the study in a manner similar to those applied in the reviewed statin trials.

Studies III and IV included only patients deemed eligible for the Special Reimbursement for diabetes. Considering the changes in both the eligibility criteria for Special Reimbursement in type 2 diabetes mellitus and in the Finnish treatment guidelines for dyslipidemia in diabetes that have taken place during the late 20th century in Finland, as well as the lack of full overlap between the two conditions, it is likely that the patients with Special Reimbursement for diabetes included in the studies are not representative for all patients with diabetes in current clinical practice in Finland. Furthermore, the Finnish patients with Special Reimbursement for diabetes may differ in their characteristics in comparison with their counterparts in other countries in and outside Europe. As Rothman and colleagues have pointed out in their article on the representativeness of observational studies, a representative study population may, in fact, be a basic requirement for generalizing the findings from descriptive studies (Rothman *et al.* 2013). However, for other observational studies, including case-control studies, Rothman and colleagues concluded that "It is not representativeness of the study subjects that enhances the generalization, it is the knowledge of specific conditions and an understanding of mechanism that make for a proper generalization" (Rothman *et al.* 2013).

The reporting in the case-control studies assessing the association between good adherence to statin use and major CVD events was concordant with the recommended reporting for observational studies as outlined in the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) statement (Vandenbroucke *et al.* 2007). In an attempt to reduce the effect of potential confounders, restriction, stratification and multivariable analysis were used and reported in the studies in accordance with the STROBE statement. However, in study III, matching was made according to gender and not with the age of the patients. This approach was chosen to allow the possibility to analyse the effect of age on the study outcome. Nonetheless, this may have resulted in residual confounding as age is an acknowledged risk factor for MCEs and it also relates with the level of adherence to statins (Mann *et al.* 2010). It was also hypothesized in Study III that stratified analyses according to CHD status at statin initiation were mandatory to control for possible confounding arising from the fact that prior CHD at statin initiation could both predict better adherence to statin therapy (Helin-Salmivaara *et al.* 2008, Mann *et al* 2010, Latry *et al.* 2011, Lemstra *et al.* 2012) and be associated with an increased risk for future CVD events in diabetes (Haffner *et al.* 1998, Schramm *et al*. 2008). However, the relative effect measures were ultimately similar in both subgroups and the whole study population (data not shown).

It was possible to investigate the potential effect of unmeasured confounders since Studies III and IV both included sensitivity analyses with the rule-out approach as recommended by the STROBE statement (Vandenbroucke *et al.* 2007). According to the sensitivity analyses it can be concluded that unmeasured confounding seems unlikely to totally explain the observed association between the high level of adherence and the incidence of CVD events.

The studies reported the association between good adherence and the incidence of CVD events primarily in relative terms. Although relative measures may be more constant between different studies, the absolute measures offer more clinically relevant data on the number of CVD events avoidable with optimal adherence to statins at the population level (Vandenbroucke *et al.* 2007). Based on absolute and relative measures in the meta-analysis conducted by Chowdhury and colleagues, it was estimated that 9% of all CVD events in Europe could be prevented with appropriate adherence to vascular medications, including statins (Chowdhury *et al.* 2013).

These studies revealed that suboptimal adherence to statin use in clinical practice is a major obstacle for obtaining the full, evidence based benefit from statin therapies in diabetes. Thus, the findings in these studies strengthen the awareness of the public health impact of poor medication adherence as has been highlighted previously (Osterberg and Blaschke 2005, Goldman and Epstein 2011, Farmer 2011). As such, these findings support initiatives which would promote the screening and management of statin adherence. However, these findings also have implications in promoting the rational use of the potentially soon-to-be-marketed, novel drug therapies for dyslipidemia currently within the "drug pipeline". Should the humanized monoclonal antibodies (mAbs) against the PCSK9 receive marketing authorizations in the Community, these study findings indicate that the mAbs should be prioritised for patients not achieving sufficient CVD prevention despite their good adherence to statin therapy.

These studies also have implications going beyond the therapies and morbidities examined in this thesis. Currently, the traditional categorical cutoff at drug approval between the confirmatory RCTs in phase III of the drug development plan and the phase IV pharmacoepidemiological studies is being revised in Europe. The adaptive licensing approaches with iterative phases of regulatory evaluation and data collection attempt to combine data from both RCTs and pharmacoepidemiological studies already at the time of market authorisation approval (Eichler *et al*. 2012). The overall aim of the adaptive licensing approach is to decrease the current uncertainty at the time of drug approval concerning the intended and unintended drug effectiveness in clinical practice. However, considering that suboptimal adherence to medications is prevalent in clinical practice, that physicians lack efficient means to detect patients with suboptimal adherence to medications (Osterberg and Blaschke 2005) and that the pharmacoepidemiological studies on intended beneficial drug effects are susceptible to major confounding by indication all mean that it is difficult to gather valid information on drug effectiveness with pharmacoepidemiological approaches for the purposes of adaptive licensing. Nonetheless, based on the results in this thesis it is reasonable to claim that combining pharmacoepidemiological register data with data derived from RCTs is essential for increasing our awareness of drug utilisation behaviour and promoting the appropriate use of evidence based medications in clinical practice. However, both the possibilities as well as the pitfalls in investigating the intended beneficial effects of drugs in clinical practice should be acknowledged both as part of interpreting the data and as part of the subsequent medical decision making.

7 CONCLUSIONS AND IMPLICATIONS

First, a substantial increase in incidence and prevalence of statin use was observed in Finland from the year 1995 to 2005. The relative increase in incidence, reflecting the prescribing patterns of the treating physicians, was most profound among the elderly and already observed before the publication of the evidence base for those aged 75 years and more. Thus, the results indicate that treating physicians were utilizing clinical trial evidence about the benefits of statins going beyond the strict eligibility criteria applied in the trials. Furthermore, no relevant gender differences were found among the statin initiators despite the fact that women had been underrepresented in the statin trials.

Second, there were limitations in the representativeness of the Heart Protection Study and the Collaborative Atorvastatin Diabetes Study for real-world diabetes care as evidenced by trial eligibility criteria and the characteristics of the trial participants. The observed limitations indicate that the physicians´ decision making on statin initiation in diabetes has been guided by other factors in addition to the reviewed trial eligibility criteria alone and reveal how the time-dependent changes in clinical diabetes care have influenced the representativeness of the landmark statin trials. Nonetheless, the similarities found in the background risk for CVD events among the real-world patients and the trial participants demonstrate the applicability of the trial findings for real-world diabetes care. In comparison to the situation in the trials, lower adherence to statin therapy and lower statin doses in the real-world, however, were found not only to limit the representativeness of the trials but are also likely to dilute the benefits.

Third, good adherence to statin use was found to associate with a decrease in the incidence of major cardiovascular events in diabetes. Although residual confounding due to unmeasured confounders may have distorted the results, it seems reasonable to conclude that appropriate adherence to statin use in clinical diabetes care is likely to result in more effective prevention of CVD events at the population level.

As a whole, these studies demonstrate the value of pharmacoepidemiology in reducing the boundaries between clinical trial evidence and real-world clinical care. Most importantly, these studies highlight the need to promote good adherence to statin use in clinical practice in order to obtain the full therapeutic value demonstrated in the statin trials. Increasing the number of statin users at the population level will not alone suffice in sharing our common resources appropriately.

APPENDIX

Glossary and a description of the Finnish drug reimbursement system (available at www.kela.fi).

Reimbursement of medicine costs: Refers to the portion of the price of a medication purchase that is reimbursed by the SII, Finland, as part of the National Health Insurance scheme. If they are to be covered by the National Health Insurance scheme, the prescription medications are required to have reimbursability and reasonable wholesale prices as approved by the Pharmaceuticals Pricing Board. A selection of over-the-counter drugs is also reimbursed provided that they have been prescribed by a physician. The Finnish medicine reimbursement system includes three categories for the reimbursed proportions of the medicine costs. The reimbursed proportions have varied over time and are currently set at 35%, 65% and 100% for the basic reimbursement, lower and higher special reimbursement, respectively.

Basic Reimbursement: Refers to the lowest fixed proportion of the costs of medicines reimbursed under the National Health Insurance scheme. The basic reimbursement covers medicines in the basic reimbursement category as outlined by the Pharmaceuticals Pricing Board. A fixed reimbursement level was set for all medications purchased under basic reimbursement until the year 2006 after which the patient was no longer obliged to pay any fixed non-reimbursable sum per purchase.

Special Reimbursement: Refers to the higher fixed proportions of the costs of medicines reimbursed under the National Health Insurance scheme. The special reimbursement covers medicines used for treating some serious and chronic illnesses that are categorised under the lower or higher special reimbursement category by the Pharmaceuticals Pricing Board. Illnesses considered eligible for special reimbursement of medication costs are outlined by the Council of State.

Generic substitution: Refers to the obligation of the pharmacy to substitute a medicinal product purchased by prescription with a cheaper alternative containing the same amount of the same active substance provided that the prescribing physician or the customer has not forbidden the substitution and that the medicinal product has been defined as a substitutable medicinal product by the Finnish Medicines Agency, Fimea.

Social Insurance Institution (SII): Administers the National Health Insurance scheme that reimburses costs for prescription medicines.

Pharmaceuticals Pricing Board: Operates under the Ministry of Social Affairs and Health and decides on which medicinal products are to be included in the reimbursement system, their wholesale prices and their refund categories. The decisions are based on the applications prepared by the Marketing Authorisation Holders.

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