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STATIN ADHERENCE, UTILISATION, AND PRESCRIBING PATTERNS

Improving effectiveness of treatment

Heli Halava

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To my loved ones:

Vesa, Vili, Minka, Vilma and Pihla

There are things known and things unknown,
in between are the doors of perception.
Aldous Huxley

ABSTRACT

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Statins are one of the most widely studied and evidence-based medications. Randomised controlled trials have provided convincing evidence on the benefits of statin therapy in preventing cardiovascular events. Despite proven benefits, low costs, and few adverse effects, everyday effectiveness of statins is limited, since adherence to statin therapy is poor.

This thesis was conducted as four pharmacoepidemiological studies using register data on statin users in real clinical care. The main purpose of the study was to evaluate prescribing patterns and to discover the lifestyle factors predicting statin nonadherence and discontinuation. This knowledge is essential in order to help physicians to motivate the adherence of their patients to treatment.

In Finland, from 1998 to 2004, the number of statin initiators nearly doubled. The discovered channelling of atorvastatin and simvastatin may have affected the treatment outcomes at the public health level. It is possible that money spent on statins in Finland in 1998–2004 could have been used in a more cost-effective way. In 2015, the percentage of patients receiving reimbursement for statins was 12% of the total population. Thus, it is a major public health and economic challenge to improve statin effectiveness and allocate therapy correctly.

Among the participants with cardiovascular comorbidities, risky alcohol use or clustering of lifestyle risks were predictors of nonadherence. In addition, the prevalence of nonadherence to statins increased after retirement among both men and women. This increase in post-retirement nonadherence was highest among those receiving statins for secondary prevention. Discontinuation of statin therapy was predicted by high patient co-payment, and in women, by risky alcohol use. Recognising the predictors of nonadherence to statins is important because nonadherence is associated with an increased risk of adverse cardiovascular outcomes and higher healthcare costs.

In conclusion, optimal outcomes in medical therapy require both efficacious medications and adherence to those treatments. When prescribing statins to eligible patients, the physician's clinical expertise in recognising patients at risk of statin discontinuation and nonadherence, as well as their ability to increase adherence, may have a great effect on public health.

Keywords: statins, adherence, nonadherence, discontinuation, prescribing, lifestyle, retirement

TIIVISTELMÄ

Heli Halava
Statiinihoitoon sitoutuminen, lääkekäyttö ja -määräykset.
Hoidon vaikuttavuutta parantamassa.

Turun yliopisto, lääketieteellinen tiedekunta
Kansanterveystieteen oppiaine ja Farmakologian, lääkekehityksen ja lääkehoidon oppiaine
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Kattavasti tutkittu ja näyttöön perustuva statiinilääkitys on oleellinen osa sydän- ja verisuonitautien ehkäisyä ja hoitoa. Satunnaistetuissa, kontrolloiduissa hoitotutkimuksissa osoitetusta tehosta, matalasta kustannuksesta ja vähäisistä haittavaikutuksista huolimatta statiinien vaikuttavuus arkielämässä jää odotettua heikommaksi, mikäli hoitoon sitoudutaan huonosti.

Tämä väitöskirja koostuu neljästä lääke-epidemiologisesta tutkimuksesta, joissa arkielämän statiinikäyttöä tutkittiin rekisteritiedon avulla. Tutkimuksen tavoitteena oli sekä selvittää statiinien käyttöä ja lääkemääräyskäytäntöjä että tunnistaa hoitoon sitoutumiseen vaikuttavia tekijöitä, jotta käytännön lääkärit voisivat lääkehoidon toteutumisen seurannassa paremmin ylläpitää potilaan hoitomotivaatiota.

Statiinilääkityksen aloittajien määrä lähes kaksinkertaistui Suomessa vuodesta 1998 vuoteen 2004. Tässä tutkimuksessa havaittu atorva- ja simvastatiinin kanavoituminen viittaa siihen, että statiineihin sijoitettu raha olisi mahdollisesti voitu Suomessa vuosina 1998–2004 käyttää kustannustehokkaammin. Vuonna 2015 statiineista sai sairausvakuutuskorvausta lähes joka kahdeksas suomalainen, minkä vuoksi statiinihoidon oikea kohdentaminen ja vaikuttavuuden parantaminen ovat merkittäviä sekä kansanterveyden että -talouden kannalta.

Tämä tutkimus osoittaa, että haitallinen alkoholin käyttö ja elämäntapariskien kasautuminen ennustivat huonoa statiinihoitoon sitoutumista niillä tutkittavilla, joilla oli aiemmin diagnosoitu sydän- ja verisuonitauti tai diabetes. Myös eläköityminen lisäsi huonosti statiinihoitoon sitoutuneiden osuutta sekä miesten että naisten joukossa. Vaikutus tuli selvimmin esiin sekundaaripreventiopotilailla. Statiinihoidon aloittaneista 12 % lopetti lääkityksen ensimmäisen vuoden aikana. Hoidon ennenaikaista lopettamista ennusti korkeampi potilaan maksama osuus lääkekustannuksesta, naisilla myös haitallinen alkoholin käyttö. Edellä mainittujen tekijöiden tunnistaminen on tärkeää, sillä huonon hoitoon sitoutumisen tai hoidon ennenaikaisen lopettamisen tiedetään lisäävän haitallisia valtimosairaustapahtumia ja terveydenhuollon kokonaiskustannuksia.

Järkevän ja ihanteellisesti vaikuttavan lääkehoidon edellytyksenä on sopivan käyttöaiheen ja sopivan lääkkeen valinnan lisäksi se, että potilas ymmärtää lääkityksensä merkityksen ja sitoutuu hoitoon. Lääkehoidon lopettamiseen tai hoitoon sitoutumattomuuteen liittyvien riskien tunnistaminen voi merkittävästi edistää kansanterveyttä.

Avainsanat: statiinit, hoitoon sitoutuminen ja sitoutumattomuus, lääkehoidon lopettaminen, lääkemääräykset, elämäntapa, eläköityminen

TABLE OF CONTENTS

ABBREVIATIONS

ASCVD	atherosclerotic cardiovascular disease
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CAD	coronary artery disease
CI	confidence interval
CK	creatine kinase
CV	cardiovascular
CVD	cardiovascular disease
CYP3A4	cytochrome P450 3A4 enzyme
DDD	defined daily dose
DRP	drug related problem
FHDR	Finnish Hospital Discharge Register
GEE	generalised estimating equation
HDL	high density lipoprotein
HMG-CoA	hydroxymethylglutaryl-coenzyme A
HR	hazard ratio
ICD	International Classification of Diseases
LDL	low dense lipoprotein
LDLR	low dense lipoprotein receptor
LFT	liver function test
LLD	lipid-lowering drug
MEMS	Medication Event Monitoring System
MET	metabolic equivalent task
MI	myocardial infarction
MPR	medication possession ratio
na	not applicable
ns	not significant
OR	odds ratio
OTC	over-the-counter, pharmaceuticals sold without prescription
PCSK9	proprotein convertase subtilisin-kexin type 9
PDC	proportion of days covered
PR	prevalence ratio
RCT	randomised controlled trial
Ref	reference
RR	relative risk
SCORE	Systematic Coronary Risk Evaluation scale
SII	Social Insurance Institution of Finland (Kela)
WHO	World Health Organization

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by the corresponding Roman numerals I-IV. In addition, some unpublished data are presented in this thesis.

I Halava Heli, Helin-Salmivaara Arja, Junnila Jouni, Huupponen Risto. Selective prescribing of simvastatin and atorvastatin by patient characteristics at treatment initiation over a 7-year period in Finland. *The European Journal of Clinical Pharmacology* 2009; 65:927-933

II Halava Heli*, Korhonen Maarit Jaana*, Huupponen Risto, Setoguchi Soko, Pentti Jaana, Kivimäki Mika, Vahtera Jussi. Lifestyle factors as predictors of nonadherence to statin therapy among patients with and without cardiovascular comorbidities. *Canadian Medical Association Journal* 2014; 186:E449-E456

III Halava Heli, Huupponen Risto, Pentti Jaana, Kivimäki Mika, Vahtera Jussi. Predictors of first-year statin medication discontinuation: A cohort study (in press *Journal of Clinical Lipidology* 2016) DOI: http://dx.doi.org/10.1016/j.jacl.2016.04.010

IV Halava Heli, Westerlund Hugo, Korhonen Maarit Jaana, Pentti Jaana, Kivimäki Mika, Kjeldgård Linnea, Alexanderson Kristina, Vahtera Jussi. Influence of retirement on adherence to statins in the Insurance Medicine All-Sweden total population database. *Public library of science (PLOS) ONE* 2015; 10:e0130901

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1 INTRODUCTION

Statins are one of the most widely studied and evidence-based medications (Taylor *et al.* 2013). They are well tolerated, safe, and due to generic substitution, also inexpensive. Despite these well-documented benefits, adherence to statins is poor and moreover, statins are commonly discontinued at least temporarily (Zhang *et al.* 2013). Discontinuation may often result in a statin-related event. Nonetheless, many of these events may have other etiologies, since most patients who reinitiate statin can tolerate it in the long-term. Thus, unnecessary discontinuation of statins (Ellis *et al.* 2004) can lead to cardiovascular events that would be preventable and it may even affect mortality.

Cardiovascular diseases are the leading cause of death worldwide. High total cholesterol together with high blood pressure, smoking, and an unhealthy diet are the major cardiovascular risk factors (Lim *et al.* 2012). Even though randomised controlled trials have provided convincing evidence on the benefits of statin therapy in preventing cardiovascular events (Reiner *et al.* 2011), a considerable proportion of patients who are prescribed statins are nonadherent, consuming less than 80% of the prescribed medication (Lemstra *et al.* 2012).

As drugs do not work in patients who do not take them, this nonadherence to statins is associated with an increased risk of adverse cardiovascular outcomes and higher healthcare costs (Osterberg, Blaschke 2005, Ho *et al.* 2009, Rasmussen *et al.* 2007). Therefore, identifying factors that affect adherence form a major public health challenge.

Contrary to randomised placebo-controlled clinical trials, which may suffer from a selection bias or exclude older subjects or patients with multiple comorbidities, the studies in this thesis are based on populations and routine clinical settings, which included all patients prescribed statins. Though almost one in ten cardiovascular events could be attributed to statin medication nonadherence (Chowdhury *et al.* 2013), more readily detectable predictors of nonadherence are required. The rationale of this thesis was to analyse using epidemiological methods a nation-wide statin utilisation and adherence to statins in Finland and Sweden, and to discover factors in relation to the decision to prescribe statins.

"*Increasing adherence may have a greater effect on health than any improvement in specific medical therapy*" (Brown, Bussell 2011)

2 REVIEW OF THE LITERATURE

Several review articles have been published on some of the topics presented in this thesis. This review of the literature is based on relevant review articles and completed with individual articles.

2.1 Adherence to medications

2.1.1 Definition

Physicians have always known that patients may not take medication according to the recommended schedule. The term *compliance* was coined in the 1970s to prevent an efficacious medication falsely being regarded as useless in a patient who had failed to take it (Feinstein 1990). The term created did not receive universal acclaim, but no other single word was then preferred as a substitute either. *Adherence, fidelity,* and *maintenance* have been used as synonyms for compliance.

Some previous studies have also used study-specific operational definitions or mixed the terms compliance, adherence, and persistence without adequate delineation. Some authors have separated compliance from persistence, but used the term adherence to combine the two sets of results (Cramer *et al.* 2008). Similarly, many reports measuring persistence call it compliance and *vice versa* (Sikka *et al.* 2005).

The term compliance indicates that a person is passively following a doctor's orders rather than actively collaborating in the treatment process. The term adherence instead, requires the person's agreement to the recommendations for therapy, and on this account, has become the preferred term. Adherence has been defined as *"the extent to which a person's behaviour– taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider"* by the World Health Organization (Sabaté 2003). Medication adherence usually refers to whether patients take their medications as prescribed (*e.g.* twice daily), as well as whether they continue to take a prescribed medication (Ho *et al.* 2009) for the prescribed length of time and this is reported as a percentage. The percentage refers to the intensity of drug use during the duration of therapy (Caetano *et al.* 2006).

Persistence, on the other hand, refers to continuity, which is the duration of time from initiation to discontinuation of the therapy (Cramer *et al.* 2008, Helin-Salmivaara *et al.* 2008, Upmeier *et al.* 2014). In the case of chronic diseases, the appropriate course of therapy may be months, years, or even the person's lifetime.

2.1.2 Implementations of adherence

Suboptimal adherence, or nonadherence, may decrease the full benefit of medications in clinical care. There is a need for cost-effectiveness studies in order to understand better the association between adherence and healthcare costs and to improve medication adherence. Many new cardiovascular therapies have been introduced to reduce morbidity and mortality, and the next challenge will be persuade patients to use these medications as prescribed (Ho *et al.* 2009).

2.1.3 Dimensions affecting adherence

"Number one predictor of a patient's medication adherence is if they believe they have a healthcare provider that cares about them" (Berger 2008)

Various factors influence adherence behaviour (Maningat *et al.* 2013) and causes of non-adherence are complex (Table 1).

Table 1. Identified predictors of nonadherence to long-term medication, modified from Gellad *et al*. 2011, Krueger *et al*. 2005, Osterberg, Blaschke 2005 and Gherman *et al*. 2011.

Cost of medication, copayment, or both	Poor provider-patient relationship
Lack of social support network	Duration of therapy
Low health literacy	Unstable living conditions
Depression / psychological problems	Psychiatric disease
Alcohol abuse	Cognitive impairment
Forgetfulness	Anger, anxiety, psychosocial stress
Lack or severity of symptoms	Lack of immediate benefit of therapy
Belief medications are harmful	Understanding why medication is needed
Complexity of medication regimen	Limited access to health care facilities
Inconvenience of medication regimen	Inadequate follow-up capacity
Actual or perceived adverse effects	Polypharmacy
Motivation	Fear of dependence

There are several ways to classify these factors. The World Health Organization (WHO) (Sabaté 2003) defines motives of decreased adherence into five categories: socioeconomic factors, factors associated with the health care system and team, disease-related factors, therapy-related factors and patient related factors (Figure 1). The focus of this thesis is on the patient-related and social factors of statin adherence.

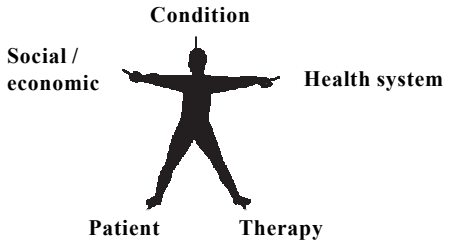

Figure 1. Five interacting factors affecting adherence**,** adopted from (Sabaté 2003)

2.1.3.1 Social and economic factors

Nonadherence may be caused by low socioeconomic status. The specific factors identified as barriers to medication adherence are high medication costs, long waiting times at the chemist, and poor understanding of medication instructions (Kripalani *et al.* 2008). Physicians need to be aware of the cost of medications, since lower statin copayments have been shown to associate with higher levels of statin adherence (Gibson *et al.* 2006, Aarnio *et al.* 2014, Helin-Salmivaara *et al.* 2012). In line with this, high incomes associate with good adherence (Chan *et al.* 2010) and low incomes with nonadherence (Mann *et al.* 2010, Benner *et al.* 2002). A long distance from the treatment centre, a lack of connections to the treatment centre, the high cost of transport as well as a low level of education, unemployment, or unstable living conditions may also all have significant effects on adherence (Sabaté 2003).

Age has been shown to predict adherence to long-term medication. As this relationship is inverted and U-shaped, age should be evaluated separately for each condition and age group. In a review of 10 studies (Mann *et al.* 2010), adherence to statins was found to be highest among patients in middle age, from about 50 to 69 years. For many elderly patients adherence to treatments is essential to prevent disability; failure to adhere to medical treatment has been found to increase disability and early death (Scandinavian Simvastatin Survival Study Group 1994). In addition, older age has also shown to associate with good adherence (Chan *et al.* 2010, Trusell, Sundell 2014, Aarnio *et al.* 2014, Pittman *et al.* 2011, Natarajan *et al.* 2007). However, it has been demonstrated that patients over 75 years of age have particularly lower rates of adherence to statins (Benner *et al.* 2002), potentially arising from poor access to health care or concomitant dementia. In addition, several studies have found that females are less likely to adhere to statin medication than men (Ye *et al.* 2007, Chan *et al.* 2010, Mann *et al.* 2010, Ellis *et al.* 2004, Pittman *et al.* 2011).

2.1.3.2 Health system-related factors

A good patient-provider relationship may improve adherence (Chan *et al*. 2010, Brookhart *et al*. 2007a, Jahng *et al*. 2005, Martin *et al*. 2005), but at the same time there are many factors in the relationship that may have a negative effect: inadequate knowledge or training of the health care providers, an overworked health care system where clinicians do not have resources to meet the patient's individual needs, the insufficient time a clinician has to spend with patients to properly assess and understand their medication-taking behaviours (Brown, Bussell 2011). Moreover, a weak follow-up capacity in the system may decrease adherence. Patients who have had more outpatient visits to a physician in the previous year have also been shown to be more adherent (Chapman *et al*. 2008). Patients' trust in their physicians is essential to their emotional revelation and important for the patient-physician relationship (Gellad *et al*. 2011). They must believe that their physician understands their unique experience of being a patient, and will provide them reliable and honest advice (Branch 2000, Martin *et al*. 2005). A retrospective cohort study using the administrative data of 14 257 patients, significantly predicted good adherence for those who had been prescribed statins by a cardiologist or the patient's primary care physician (Chan *et al*. 2010).

Health information technology does not facilitate physicians' access to information concerning patients from different care related sites, which in turn compromises patient care (Brown, Bussell 2011).

2.1.3.3 Condition-related factors

The severity of symptoms and the disease, the level of disability, the rate of progression of the disease, and the availability of effective treatments are strong determinants of adherence (Sabaté 2003). Comorbidities, such as a diagnosis of hypertension or diabetes (Mann *et al.* 2010), have associated with better adherence, although diabetes (Donnelly *et al.* 2008) and depression (DiMatteo *et al.* 2000, Benner *et al.* 2002, Ye *et al.* 2007) have also predicted nonadherence. Depression can cause pessimism, cognitive impairments, and withdrawal from social support, all of which can reduce both the readiness and ability to follow treatment instructions. In addition, alcohol (Bryson *et al.* 2008) or drug abuse may be important modifiers of adherence behaviour. Finally, patients with more cardiovascular risk factors or patients with a history of cardiovascular disease (Mann *et al.* 2010, Trusell, Sundell 2014, Pittman *et al.* 2011, Aarnio *et al.* 2014) tend to have better adherence to statins.

2.1.3.4 Therapy-related factors

The most notable therapy-related factors associated with lower levels of adherence are those related to the complexity of the medical regimen (Choudhry *et al.* 2011), the duration of the treatment, previous treatment failures, and frequent changes in treatment. The immediacy of beneficial effects, the experience of side-effects, and the availability of medical support all have an impact on adherence (Sabaté 2003). Concerns about medication typically arise from beliefs about adverse effects (Mann *et al.* 2007) and from more abstract worries about the long-term effects and dependence. These fears are related to negative views about medicines as a whole and suspicions that doctors over-prescribe medicines. Some studies (Chapman *et al.* 2008) have reported a negative association between taking more drugs and adherence (*i.e.* a greater number of drugs being associated with worse adherence). On the other hand, in a prospective cohort study using pharmacy claims (Gazmararian *et al.* 2006), those who took more than three medications had a significantly lower probability of nonadherence compared to those taking three medications or less (odds ratio [OR] 0.77, 95% confidence interval [CI] 0.73–0.95). In addition, taking four to six other medications has been a significant independent predictor of high adherence (OR 2.69, 95% CI 1.37–5.29) in a patient self-report survey (Natarajan *et al.* 2007). Simple dosing (one pill, once daily) has been shown to increase adherence (Claxton *et al.* 2001).

2.1.3.5 Patient-related factors

Patients must be aware of the health risk related to their disease and understand the treatment instructions before they can follow medical recommendations (Gherman *et al.* 2011). In relation to statin treatment, instructions are typically very simple: once daily. As a whole, patient-related factors represent the resources, knowledge, attitudes, beliefs, perceptions and expectations of the patient (Sabaté 2003) and patients' health literacy is central to their ability to adhere (Martin *et al.* 2005, Gellad *et al.* 2011). Some patient-related factors that have been reported to affect adherence are forgetfulness, psychosocial stress (Molloy *et al.* 2008) and anxieties about possible adverse effects (Zhang *et al.* 2013, Gellad *et al.* 2011, Krueger *et al.* 2005). The patient's knowledge and acceptance of their disease, confidence, expectations or negative beliefs regarding the efficacy of the treatment, their previous experiences with pharmacological therapies, and lack of motivation all influence the patient's adherence behaviour (Osterberg, Blaschke 2005, Sabaté 2003) in ways not yet fully understood.

Patients' involvement and participation in their care can enhance adherence and provide satisfaction (Martin *et al.* 2001, Martin *et al.* 2003); patients who want to be involved tend to

ask more questions. This kind of reciprocal or concordant relationship facilitates the understanding of a patient as regards the costs and benefits of their treatments and is vital to actively involve the patient (Martin *et al.* 2005, Elwyn *et al.* 2003). Additionally, a Canadian family practice study using patient self-report (Natarajan *et al.* 2007) has shown lifestyles including regular exercise or a healthy diet (OR 3.18, 95% CI 1.41–7.16) to be a significant independent predictor of a high adherence score.

2.1.4 Importance of adherence

"Drugs don't work in patients who don't take them." (Osterberg, Blaschke 2005, Ho *et al.* 2009)

Poor adherence should always be considered when a patient's condition is not responding to medical treatment. According to the WHO "Increasing adherence may have a greater effect on health than any improvement in specific medical therapy". Inadequate medication adherence is a growing concern to clinicians, and in healthcare systems, as well as to other stakeholders (such as payers) because of mounting evidence that nonadherence is prevalent and associated with adverse outcomes and higher costs of healthcare (Osterberg, Blaschke 2005).

Previous studies have shown statins to be effective in primary prevention of cardiovascular diseases (Taylor *et al.* 2013) but adherence appears to have a major impact on the cost-effectiveness of the treatment (Aarnio *et al.* 2015). This finding emphasises the importance of adherence in obtaining the full benefit of the investment in statins.

Nonadherence can increase healthcare costs, decrease patient productivity and their quality of life. As there are a multitude of reasons for nonadherence, it requires a patient-centered approach to manage it and the achievement of longer-term therapeutic and outcome goals require a partnership with patients (Ho *et al.* 2009). Many observational studies have evaluated the associations between medication adherence and outcomes. They reinforce the benefits of cardiovascular medications and highlight the importance of adherence in order to optimise patient outcomes. For example, in secondary prevention, nonadherence to statins was associated with a 12–25% relative hazard increase in mortality (Rasmussen *et al.* 2007). Similarly, for statin medications, each incremental 25% increase in the proportion of days covered was associated with a 3.8 mg/dL (equals 1 mmol/l) reduction in low dense lipoprotein (LDL) cholesterol (Ho *et al.* 2006).

Thus, compared with adherent patients, nonadherent patients with hypertension have a 5.4 times higher risk for hospitalisation, rehospitalisation, and premature death, and those with dyslipidemia a 2.8 times higher risk, and 1.5 times higher if they have heart disease (Claxton *et al.* 2001).

2.1.5 Measuring of adherence

Adherence is related to individual patient behaviour and consequently, the measurement of medication adherence is challenging. No method is considered the gold standard as each method has advantages and disadvantages. Currently, combinations of the following measures are used to assess adherence behaviour. In addition to monitoring the outcome, these tools facilitate researchers in evaluating medication adherence.

Adherence measurement methods can be categorised as either direct or indirect (Osterberg, Blaschke 2005). The direct methods are biochemical measurements obtained by adding a nontoxic

marker to the medication and detecting its presence in blood or urine, or the measurement of serum drug levels typically used in pharmacological research. Furthermore, the amount of topical medications, such as creams consumed during a treatment period, has been weighed to measure adherence. The direct methods are expensive, not practical for routine clinical use, and will only be presented in outline in this thesis. The Helsinki Heart Study (Maenpaa *et al.* 1992) employed three adherence estimation methods: capsule counting every three months, urine gemfibrozil analysis every six months, and a digoxin marker added to both the gemfibrozil and placebo capsules at the end of the third and fifth study years. The latter two of these methods (gemfibrozil analysis and digoxin marker technique) can be considered to be direct methods.

Indirect methods (Table 2) can be subdivided into interviews and registers. The most commonly used indirect methods are patient self-report, pill counts, and prescription renewals. In the literature, one of the most frequently used methods is *electronic pharmacy prescription data*, which requires that patients obtain their medications within a closed pharmacy system. While the history of patient's renewals does not account for taking the medication the correct way, this method provides readily available, objective, and accurate measurements of pharmacy purchases. In Nordic countries, the completeness and accuracy of pharmacy records are high as all information about drugs dispensed and purchased by patients is entered into national databases. Records of prescription renewals have been found to be highly correlated with a broad range of patient outcomes (Ho *et al.* 2008). Based on pharmacy data, a variety of methods have been used to estimate adherence (Andrade *et al.* 2006, Hess *et al.* 2006, Vink *et al.* 2009). The two most commonly used measures of medication adherence using prescription renewals are the medication possession ratio (MPR) and the proportion of days covered (PDC) methods. They are both usually reported as percentages and defined by the number of assumed doses dispensed in relation to a pre-specified dispensing period (Ho *et al.* 2009). The main difference between these two measures is that the maximum PDC is 1.0, which indicates full adherence, whereas the MPR accounts for oversupplies and can have a value >1.0 (Hess *et al.* 2006, Andrade *et al.* 2006). Although MPR has been more commonly used, PDC is becoming the preferred adherence measurement because of its advantages.

MPR is the sum of the days' supply for all dispensed drugs in a particular time period, divided by the number of days in the same period. This calculation is simple but in many cases, overestimates adherence; for example for patients, who routinely renew their medications early. Due to different denominators, these ratios cannot be combined across participants. To provide an overall study adherence value, the ratios has to be divided and averaged.

PDC is a newer record-based method of recording prescription adherence. It has been used in scientific literature with increasing frequency, since instead of simply adding the days' supplied in a given period, the PDC considers the days that are "covered" with the medication. This means that the overlapping days supply (new dispensation date before the preceding purchase void consumed) will be moved forward to the end of supply date of the previous dispensation to provide a true picture of the days on which a patient is covered with medication (Murphy *et al.* 2015). The PDC is calculated as the number of days with the drug on hand divided by the number of days in the specified time interval (*e.g.* 180 or 365 days). The numerator of the PDC is not only a sum of the "days supplied" by all prescriptions filled during the period but filled prescriptions are evaluated using a set of rules to avoid double-counting of the days covered. Thus, the PDC is always a value between 0 and 1 or 0 to 100%.

However, the measure of prescription renewals does not capture nonadherence when the dispensed medications are not used. In addition, the MPR and PDC measurements of medication adherence correlate well with the quantity of doses taken but not with the timing of

the doses. If the length of follow-up varies between patients, the assessment of adherence with these measures is more difficult (Choo *et al.* 1999). In future, the use of technology may enable more direct measurements and provide an aspect of dose-by-dose adherence.

Defined daily dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults (WHO 2009a). It is not a recommended or prescribed dose but a technical unit of comparison. The DDDs may be too high or too low relative to the actual prescribed doses and they do not take into account variations in adherence. Duration of statin prescriptions has been estimated with assumed doses or a dose equal to DDD per day because many of the databases lack information on prescribed doses. A recent study based on claims data in Finnish chemists (Romppainen *et al.* 2014) indicated that the duration of statin prescriptions can be validly estimated by assuming a daily dose of one unit per day and that the assumed dose of DDD per day would, actually, most likely either over- or underestimate this duration.

Adherent users are commonly referred to as those with a PDC ≥80%. Nonadherents, respectively, are referred to using the conventional cut-off point of the dichotomy (PDC by treatment <80%). This percentage division, although somewhat arbitrary, has been accepted as the most conventional and widely reported cut-off for optimum adherence (Chowdhury *et al.* 2013, Benner *et al.* 2002, Perreault *et al.* 2009a, Perreault *et al.* 2009b). Although this division appears practical for cardiovascular medications, a recent analysis has revealed that there continues to be reductions in LDL cholesterol and blood pressure when the adherence levels go beyond 80% (*e.g.* 80% to 100%), which demonstrates that the optimal level of adherence may be higher than the current cut-offs (Ho *et al.* 2009). There is no real consensus on the optimal level of adherence. Understandably, for certain other medications, such as oral contraceptives, the 80% cut-off may be too low.

Table 2. Indirect methods of measuring adherence, modified from Osterberg, Blaschke 2005 and National Collaborating Centre for Primary Care (UK) 2009.

Method	Advantages	Disadvantages
Rates of prescription renewals	Objective, easy to obtain data	Requires a closed pharmacy system, not equivalent to ingestion of medication
Patient self-reports, questionnaires	Inexpensive, simple, quick and easy, those reporting nonadherence are likely truthful	Susceptible to error and recall bias, patient may garble results and overestimate adherence
Pill counts	Objective, easy to perform	Easily altered by patient; patient can discard pills
Electronic medication monitors	Objective, precise, easily quantified	Expensive
Measurement of physiologic marker	Easy to perform	Other factors (absorption, metabolism) can affect the result
Patient diary	Easy to perform	Easily altered by the patient
Assessment of clinical response	Relatively easy to perform	Many factors other than medication need to be taken into account

Subjective measurements or self-reports (Table 3) obtain information by asking patients, family members, caregivers, and physicians about the patient's medication use and utilise different interview tools to determine drug-related problems (DRP). Objective measurements obtain information by counting pills, examining records of prescription renewals, or using electronic technologically-oriented tools, such as Medication Event Monitoring System (MEMS). The MEMS system utilises a hidden microchip mechanism, which records the time and date that a patient opens a pill box or removes a pill from a pack (Farmer 1999).

Table 3. Four examples of different self-assessment questionnaires used to measure adherence, modified from Morisky *et al*. 2008, Raehl *et al*. 2002 and Lee *et al*. 2009.

Morisky 8-item scale	**Morisky 4-item scale**	**Raehl's Med Take**	**Timer DRP**
Cardiovascular medications		**In the elderly**	**Non-threatening**
1. Do you sometimes forget to take your pills?	1. Do you ever forget to take your medicine?	1. Demographics	1. Everyone forgets to take their medicines. How often does this happen to you?
2. Over the past two weeks, were there any days when you did not take your medicine?	2. Are you careless at times about taking your medicine?	2. Medical history	2. Everyone says that they miss a dose of their medication or adjust it to suit their own needs. How often do you do this? Why?
3. Have you ever cut back or stopped taking your medication without telling your doctor because you felt worse when you took it?	3. When you feel better do you sometimes stop taking your medicine?	3. Medication history: prescriptions (pillboxes or calendar boxes), over-the-counter pharmaceuticals and herbal preparations	3. Has your physician told you to change how you take any of your medications?
4. When you travel or leave home, do you sometimes forget to take your medications along?	4. Sometimes if you feel worse when you take the medicine, do you stop taking it?	4. Patients are asked to open a container and simulate taking the drug	4. Has your physician told you to stop taking any of your medications?
5. Did you take your medicine yesterday?			
6. When you feel like your disease is under control, do you sometimes stop taking your medicine?			
7. Taking medication every day is a real inconvenience for some people. Do you ever feel harassed about staying with your treatment plan?			
8. How often do you have difficulty remembering to take all your medication?			

Firstly, among self-reports *The Morisky 4-item* and *8-item scales* (Morisky *et al.* 2008) have been shown to be predictive of adherence to cardiovascular medications (such as statins) and blood pressure control (Morisky *et al.* 1986, Shalansky *et al.* 2004). Secondly, in the elderly, *Raehl's Med Take Interview* has been used to identify problems with therapy adherence (Raehl *et al.* 2002). Thirdly, *Timer DRP identification tool* is worded in a non-threatening way to give the patient a "permission" to have less than perfect adherence. This has been done in order to help patients to be open and honest (Lee *et al.* 2009) (Table 3).

In addition, a phenomenon called “white-coat adherence” has to be taken into account. This means that in a comparison of the 30-day period after an appointment with a health care provider, patients commonly improve their medication-taking behaviour in the five days before and after an appointment (Feinstein 1990).

In summary, certain methods may be preferred in specific settings but a combination of measures maximises accuracy (Osterberg, Blaschke 2005).

2.2 Public health perspective on adherence to cardiovascular medications

Optimal outcomes in population health require both efficacious treatments and adherence to those treatments. Patients, health care providers, and policy-makers, have a common aim in ensuring that effective medications for chronic illnesses are used as prescribed. Across diseases, adherence is the single most important modifiable factor that jeopardises treatment outcome. An understanding of basic behavioural principles and models of behavioural change is relevant to adherence to the treatment of all chronic medical conditions (Sabaté 2003). Atherosclerosis is associated with a large proportion of cardiovascular diseases (CVD), for example coronary heart disease (such as heart attack), cerebrovascular disease (such as a stroke) and diseases of the aorta and arteries, including hypertension and peripheral vascular disease (WHO, World Heart Federation and World Stroke Organization. 2011). Atherosclerosis develops over many years when cholesterol and fatty materials are deposited inside arteries to form lumen narrowing plaques and trigger the formation of blood clots.

CVDs are the leading causes of death and disability worldwide, most of which could be prevented. However, the preventive measures are inadequate and the number of those with these diseases continues to rise (WHO, World Heart Federation and World Stroke Organization. 2011). Globally, the majority of CVD deaths are due to ischaemic heart disease (in 2008, out of 17.3 million cardiovascular deaths, heart attacks were responsible for 7.3 million) and cerebrovascular disease (in 2008, 6.2 million deaths caused by a stroke). In Europe, there are almost 4.1 million CVD deaths / year. Of these, approximately 1.8 million people die of coronary heart disease and 1.1 million of a stroke (Nichols *et al.* 2013).

The major cardiovascular risk factors include high blood pressure, smoking, unhealthy diet (excessive use of salt, fat and calories), and high total cholesterol (Lim *et al.* 2012). The most important behavioural risk factors account for 80% of atherosclerotic coronary heart disease and cerebrovascular disease and include smoking, physical inactivity, unhealthy diet and harmful use of alcohol (Figure 2). Among the metabolic risk factors the most important are hypertension, diabetes, hyperlipidemia and overweight/obesity. In addition to these main factors, educational status, age, gender, genetic disposition and psychological factors (depression, stress) can also play a role in the etiology of atherosclerosis.

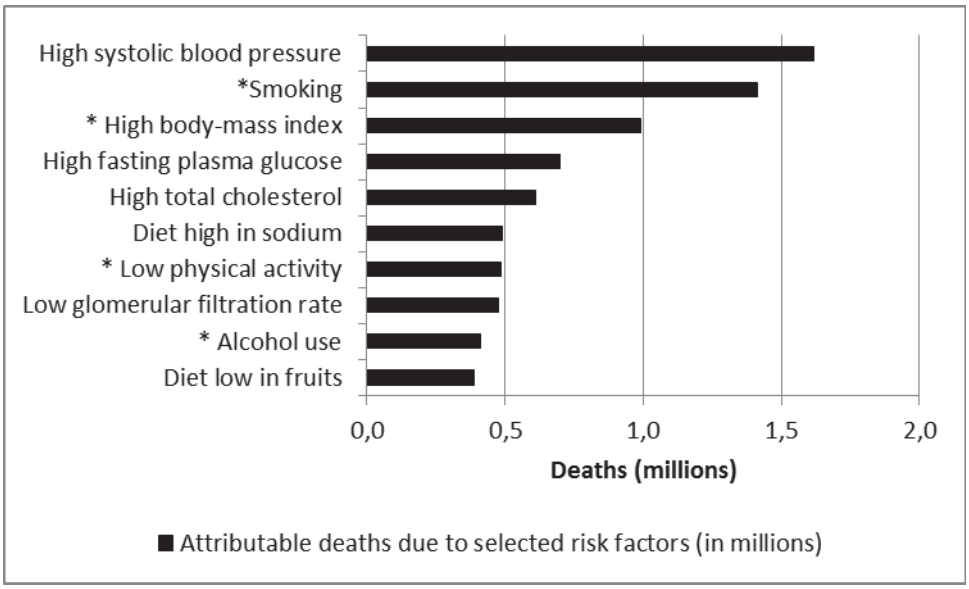

Figure 2. Ranking of selected risk factors: Of a total of 9.48 million deaths these were the 10 leading risk factor causes of death in high income countries (Gross National Income per capita ≥ USD 12 276, which was around 9171 euros in 2010). Based on the Global Burden of Diseases study 2013. http://vizhub.healthdata.org/gbd-compare/#
* This was also observed in this thesis

Statins are one of the most widely studied and evidence-based medications (Taylor *et al.* 2013) and an essential component in preventing cardiovascular diseases. Despite this evidence, over 40% of the patients prescribed statins are nonadherent, consuming less than 80% of the prescribed medication. This nonadherence translates in Europe to 9 extra cases of major cardiovascular events/100 000 individuals annually (Chowdhury *et al.* 2013). A recent meta-analysis of 44 epidemiologic studies indicated that almost one in ten cardiovascular events (approximately 9% in Europe) can be attributed to medication nonadherence (Chowdhury *et al.* 2013).

Based on the above-mentioned findings, identifying factors that affect adherence form a major public health challenge.

2.2.1 Prevention

Worldwide, there is a clear vision on reducing CVDs. Firstly, the epidemic of CVDs should be monitored. Cardiovascular mortality changes rapidly over time as societies change lifestyles on the basis of socio-economic developments, and because of this fact there is great potential for CVD prevention (De Backer *et al.* 2015). Secondly, exposure to risk factors should be prevented. Smoking remains a major cause of concern both in primary and secondary prevention of CVD. In addition, there is a need to rapidly evaluate the health effects of e-cigarettes (Vardavas *et al.* 2015). Furthermore, the importance of physical exercise has been explained in recent European and US guidelines on lifestyle and CVD prevention (Perk *et al.* 2012, Eckel *et al.* 2014). Thirdly, equitable health care for people with CVDs should be available (WHO, World Heart Federation and World Stroke Organization. 2011). In addition,

there are ongoing intervention studies to test the efficacy of the polypill to improve long-term adherence (Castellano *et al.* 2014).

2.2.2 Medical treatment

To prevent diseases, it is necessary to identify their causes and risk factors. Each risk may have roots in a complex chain of events; consisting of socioeconomic, environmental and behavioural factors (WHO 2009b). Figure 3 illustrates the major causes of ischaemic heart disease. Some of these (blood pressure, cholesterol, diabetes) act relatively directly as a cause of the disease, while others (smoking, overweight, physical inactivity, fat intake, alcohol) act indirectly. The most distal risk factors are more likely to have amplifying effects. Population-based strategies aim at an increase in healthy behaviour and a reduction in health risks. Additionally, on an individual level, medications, for example, for high blood pressure, high cholesterol or high blood glucose can be used.

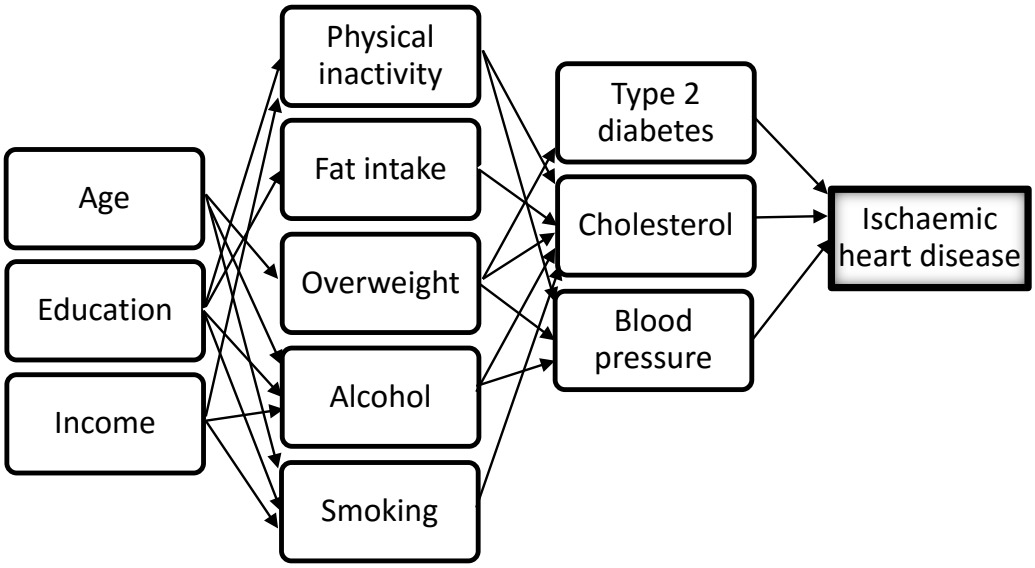

Figure 3. The causal chain of ischaemic heart disease. Only major causes and some of the interacting pathways are shown, modified from the WHO report 2009b: Global health risks: mortality and burden of disease attributable to selected major risks.

Randomised controlled trials have provided convincing evidence as to the benefits of statin therapy in preventing cardiovascular events (Reiner *et al.* 2011). According to the Framingham Study, there is a correlation between average serum cholesterol values, mainly LDL, and the occurance of CVD events (Castelli 1984), but an inverse association between high density lipoprotein (HDL) and CVD events (Gordon *et al.* 1989). Dyslipidemia guidelines recommend focusing on the total cardiovascular risk, as a result of which a decision to prescribe a statin typically involves evaluation of the patient's lifestyle (body mass index, smoking status, alcohol use and physical activity). High-risk individuals can be detected on the basis of established CVD, diabetes, severe renal disease, or a high risk score (Perk *et al.* 2012).

Risk calculators are recommended for asymptomatic adults without evidence of CVD. The purpose of these tools is to identify patients who can be helped by preventive medication and to avoid both under- and overtreatment (Perk *et al.* 2012). The most widely used risk assessment tools are the Framingham risk model (Anderson *et al.* 1991) and the Systematic Coronary Risk Evaluation (SCORE) scale (Conroy *et al.* 2003). However, the 2013 guidelines of the American College of Cardiology and the American Heart Association recommend a new risk calculator. This atherosclerotic cardiovascular disease (ASCVD) risk calculator includes age, gender, race, total cholesterol, HDL cholesterol, systolic blood pressure and treatment for high blood pressure, diabetes status, and smoking status (Stone *et al.* 2014).

Framingham Risk Score is an online assessment tool intended as a clinical practice aid for use by experienced healthcare professionals. It uses information from the Framingham Heart Study to predict a person's chance of developing cardiovascular disease in the next ten years, modified for family history. Age, gender, total and HDL cholesterol, smoking, diabetes status, systolic blood pressure and treatment for high blood pressure are used for risk assessment.

The SCORE scale estimates ten year risk of fatal CVD and uses age, gender, blood lipids, blood pressure, and smoking as predictors of the risk. There are two SCORE versions created for high- and low-risk European countries. A SCORE low-risk model is used for example in Sweden, Finland, Denmark, and Norway.

2.3 Health behaviour and retirement

People live longer after retirement age than ever before. In the period 1950-1955, the annual rate of increase in the population over 60 years and the annual rate of the total population were both around 1.8 per cent. By 2025-2030, the population over 60 years of age will be growing 3.5 times as rapidly as the total population (2.8 per cent compared to 0.8 per cent (Figure 4)) (United Nations 2015). In Western Europe, life expectancy at the age of 65 years has increased by about a third since 1970, although considerable differences across and within countries exists (Doyle *et al.* 2009). Healthy life expectancy at the age of 65 varies among countries and between the genders even more than life expectancy (Jagger *et al.* 2008). Although people tend to live longer they do not always do so in good health.

Retirement is one of relevant life transitions that can change many aspects of life, including daily routines, desires, income, social networks, and also affect the continuity of treatment. A large cohort study has shown retirement to associate with a substantial decrease in the prevalence of suboptimum health (Westerlund *et al.* 2009). This prevalence increased faster before retirement than after, which demonstrates that perceived health problems are greatly relieved by retirement. This perception of reduced symptoms of ill health can increase the likelihood of nonadherence to prescribed treatment regimens or healthy lifestyles. Relief from work-related strain, increased sleep duration as well as more frequent physical exercise appears to be the key mechanisms through which retirement affects health (Eibich 2015).

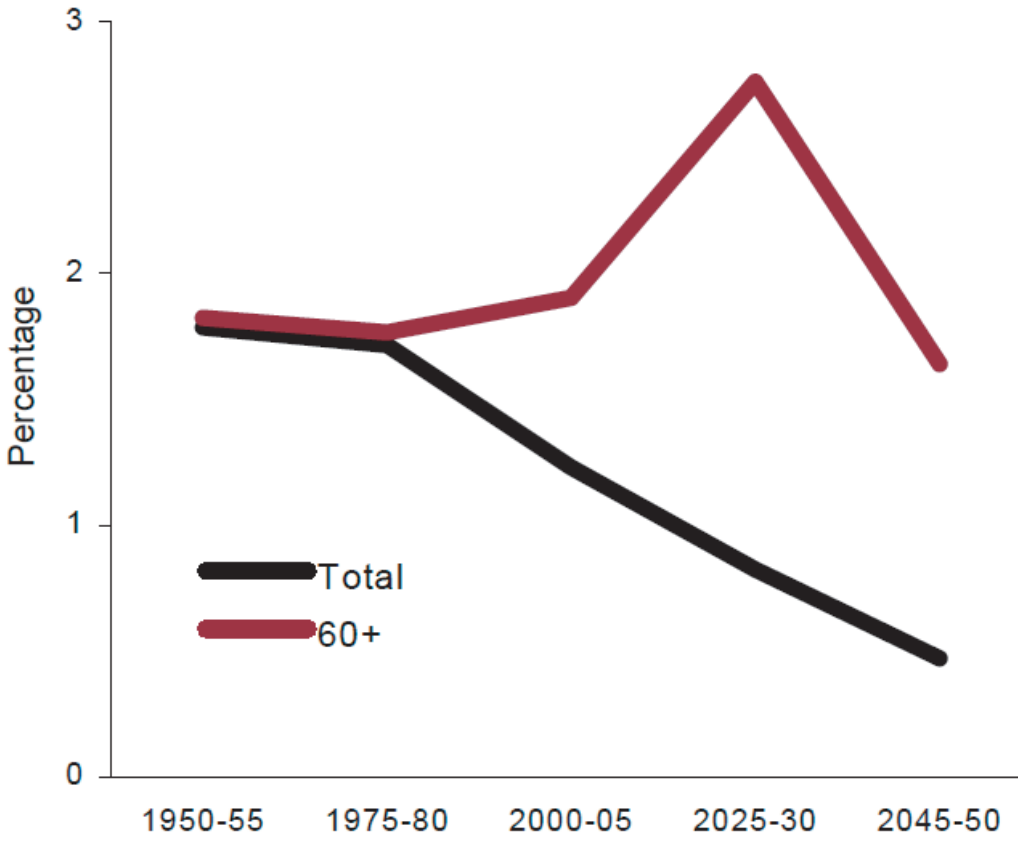

Figure 4. Average annual growth rate of total population and population aged 60 or over: world 1950-2050, adopted from United Nations 2015: World Population Prospects: The 2015 Revision.

2.4 Statins

2.4.1 Mechanism of action

Cholesterol plays a role in the synthesis of steroid hormones and bile acids. In addition, it is necessary for the synthesis of vitamin D, which is needed in the absorption of calcium. Statins act by competitively inhibiting the hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase. This impedes the HMG-CoA reductase from catalysing the conversion of HMG-CoA to mevalonate, which is the rate-limiting step in cholesterol synthesis. This triggers increased expression of hepatic LDL receptors, which clear LDL and LDL precursors from the circulation and reduces the serum LDL concentration the most (Maron *et al.* 2000) (Figure 5). The serum LDL concentration decrease is dependent on statin dose and statin type (Law *et al.* 2003). The intensive-dose statin therapy has shown to reduct cardiovascular deaths (OR 0.86, 95% CI 0.75–0.99), myocardial infarctions (MI) (OR 0.84, 95% CI 0.76–0.93), and strokes (OR 0.82, 95% CI 0.72–0.94) (Silva *et al.* 2007). A systematic review and meta-analysis of 75 randomised

controlled trials (RCTs) reporting comparisons on statins concluded that a daily dose of atorvastatin 10 mg, fluvastatin 80 mg, lovastatin 40–80 mg, or simvastatin 20 mg could decrease LDL cholesterol by 30–40%. The reduction of LDL by more than 40% was achievable only with rosuvastatin or atorvastatin at a daily dose of ≥20mg (Weng *et al.* 2010). Additionally, statins increase HDL and decrease triglycerides but to a lesser degree (Weng *et al.* 2010).

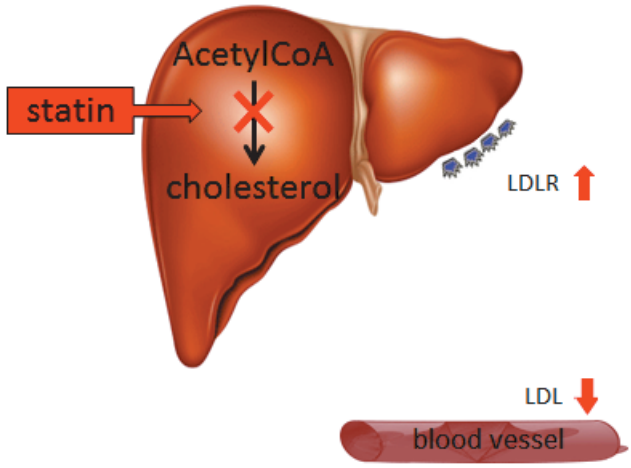

Figure 5. Statins inhibit endogenous cholesterol synthesis in the liver and upregulates LDL-receptors (LDLR) thus decreasing blood LDL.

2.4.2 Types of statins

On the Finnish drug market, there are six statins available at present: atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin (Table 4). Statins can be classified into water-soluble (pravastatin and rosuvastatin) and lipid-soluble (lipophilic) statins. The most lipophilic statins are lovastatin and simvastatin, followed by atorvastatin and fluvastatin. The first statin, lovastatin, was granted market authorisation in 1987. In Finland, simvastatin was introduced in 1992, and has been the most used statin since 1997. In 2015, it accounted for 44% of total statin consumption as expressed in DDDs (Table 5) (Voipio, T., The Finnish Medicines Agency Fimea, personal communication). Use of atorvastatin steadily increased following its introduction in 1998 and in 2015 it accounted for 36% of statin consumption. Fluvastatin, lovastatin, pravastatin, and rosuvastatin have been clearly smaller players on the Finnish market. The seventh statin, cerivastatin, was withdrawn from the drug market in 2001 due to deaths attributed to rhabdomyolysis and subsequent kidney failure. The use of cerivastatin was small prior to its withdrawal.

Table 4. The anatomical therapeutic chemical (ATC) codes (based on 2011 version) used to identify statins in the Prescription Register.

Statin	ATC code	Marketing authorisation in Finland
simvastatin	C10AA01	1992
lovastatin	C10AA02	1987
pravastatin	C10AA03	1996
fluvastatin	C10AA04	1996
atorvastatin	C10AA05	1997
rosuvastatin	C10AA07	2003

Table 5. Sales statistics in Finland: HMG-CoA reductase inhibitors (C10AA) in 2015, based on The Finnish Medicines Agency Fimea (personal communication Voipio, T.).

	DDD dosage	DDD/1,000 inh*/day	Proportion (%)
All statins (C10AA)		101.31	100.0%
Simvastatin	30mg	44.42	43.8%
Lovastatin	45mg	0.54	0.5%
Pravastatin	30mg	2.34	2.3%
Fluvastatin	60mg	2.61	2.6%
Atorvastatin	20mg	36.67	36.2%
Rosuvastatin	10mg	14.73	14.5%

* Consumption expressed as a number of Defined Daily Dose (DDD) per 1000 inhabitants per day.

2.4.3 Efficacy and effectiveness

An RCT is the golden standard method in studying efficacy and adverse effects of medication. Large double-blind RCTs have illustrated statins to be effective in reducing cardiovascular (CV) events regardless of pre-existing CVD. A meta-analysis of 199 721 participants in 92 placebo-controlled and active-comparator trials concluded that across all populations, statins were significantly more effective than the control in reducing all-cause mortality (OR 0.87, 95% CI 0.82–0.92) and major coronary events (OR 0.69, 95% CI 0.64–0.75). In participants with CVD, statins significantly reduced the number of deaths (OR 0.82, 95% CI 0.75–0.90) and major coronary events (OR 0.69, 95% CI 0.62–0.77) (Naci *et al.* 2013). In a prospective meta-analysis of data from 90 056 individuals in 14 randomised trials, statins were shown to reduce the relative risk (RR) per 1 mmol/l reduction in LDL cholesterol as follows: 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 strokes by 17%, when compared to a placebo (Baigent *et al.* 2005). In this meta-analysis, the protective effect was observable after the first year, increased over time, and safely reduced incidences of major coronary events, coronary revascularisation, and strokes throughout the 5-year period—irrespective of the initial lipid profile or other presenting characteristics.

Large, double-blind clinical trials have created the basis for clinical treatment guidelines (Reiner *et al.* 2011, Perk *et al.* 2012). However, in these trials the selection of patients is often too limited or the period of time too short to detect all the relevant adverse affects or to study drug utilisation. Efficacy in these trials refers to the treatment effect in a carefully selected and

controlled setting and therefore there is an issue of generalisability. In contrast, observational studies reflect routine clinical practice and enable long follow-up periods.

An important strength of observational, pharmacoepidemiological cohort, case-control or cross-sectional studies is their generalisability to large populations and the possibility to obtain data on effectiveness, which refers to the treatment's effect in the general population. Moreover, it is possible to minimise the exclusion criteria and include patients with multiple confounding complications, wide age ranges, various socioeconomic backgrounds, different healthcare attitudes, and concomitant medications (Atar *et al.* 2015). Several register based studies have demonstrated association between adherent statin use and CVD prevention in real-world patients. In a primary prevention study of 171 535 participants, PDC>80% predicted a decrease in major coronary events (hazard ratio [HR] 0.59, 95% CI 0.53–0.66 for women and HR 0.60, 95% CI 0.56–0.64 for men), CVD events for all (HR 0.64. 95% CI 0.60–0.67) and MI (HR 0.39, 95% CI 0.35–0.43) when compared to PDC<20% (Shalev *et al.* 2012). Another primary prevention study observed decreased rates of ischemic heart disease events (HR 0.81, 95% CI 0.71–0.94) with PDC>75% in comparison to PDC <25% (Corrao *et al.* 2010). In a population-based secondary prevention study of 17 823 acute myocardial infarction survivors, after adjustment for baseline patient characteristics, compared with those with good adherence to statins (PDC ≥80%), the risk of mortality was 12% higher among patients with intermediate (PDC 40%–79%) adherence (HR 1.12, 95% CI 1.01–1.25) and 25% higher among patients with poor (PDC <40%) adherence (HR 1.25, 95% CI 1.09–1.42) (Rasmussen *et al.* 2007).

One population study of 683 236 participants with and without pre-existing CVD has shown all-cause mortality (RR 0.42, 95% CI 0.37–0.47) and coronary heart disease mortality (RR 0.54, 95% CI 0.46–0.64) to decrease with statin adherence ≥80% in comparison to no statin use (Haukka *et al.* 2012). Another study has shown decrease in all-cause mortality, acute MI or stroke (HR 0.61, 95% CI 0.54–0.71) with PDC >80% in comparison to PDC 21–40% (Degli Esposti *et al.* 2012).

2.4.4 Adverse effects

As a class, statins are well tolerated, and there are no known differences in safety. However, statin-related events are commonly reported and they can lead to inappropriate discontinuation of medication. Moreover, most patients who reported intolerance to statin therapy were able to tolerate it long-term after being rechallenged (Zhang *et al.* 2013). As with a patient on any drug, the risk-benefit balance of treatment should be reassessed when possible adverse effects arise. These effects occurred more on statin medication when compared to placebo (OR 1.4, 95% CI 1.09–1.80, p=0.008) (Silva *et al.* 2006). For statins, a range of sources support a dose dependence, although there may also exist none dose dependent adverse effects (Silva *et al.* 2006) (Table 6). A meta-analysis comparing the incremental risks associated with intensive- and moderate-dose statin therapy demonstrated that an intensive-dose statin therapy predicted increased odds of adverse effects leading to discontinuation of the statin therapy when compared to moderate-dose statin therapy (OR 1.28, 95% CI 1.18–1.39, p<0.001) (Silva *et al.* 2007). According to this meta-analysis, moderate-dose statin therapy may be the most appropriate choice for achieving CV risk reduction in the majority of individuals, whereas intensive-dose statin therapy can be reserved for high risk patients (Silva *et al.* 2007).

Table 6. Adverse effects commonly related to statins and their dose dependency.

Adverse effect	Comment	Reference
Subjective symptoms		
Muscle effects generally	Reported incidence low in clinical trials, higher in studies of real world use. Cramps, stiffness, pain during rest and tendinitis reported. Significant dose-dependency.	Golomb, Evans 2008, Silva *et al*. 2006, Sirtori *et al*. 2012, Taylor, Thompson 2015.
Laboratory test changes		
Creatine kinase (CK) elevation	Meta-analysis has shown a significant increase in CK elevation with high-dose statins. The odds appeared to be greater for lipophilic statins, which can more readily enter muscle tissue.	Ballard *et al*. 2013, Silva *et al*. 2006, Silva *et al*. 2007.
Liver function test (LFT) elevation	Meta-analyses of RCTs have shown significant increases in LFTs with statin versus placebo. Greater for high-dose and hydrophilic statins which are actively taken up by the liver.	Golomb, Evans 2008, Kashani *et al.* 2006, Maron *et al.* 2000, Silva *et al.* 2006, Silva *et al.* 2007.
Diabetogenic effect	At meta-analysis level of RCTs, a 9% increased risk for incident diabetes. Population based cohort study concluded that treatment with higher potency statins might be associated with an increased risk of new onset diabetes.	Carter *et al.* 2013, Cederberg *et al*. 2015, Finegold *et al.* 2014, Golomb, Evans 2008, Robinson 2015, Sattar *et al.* 2010.
Proteinuria	Mild, transient, dose-related proteinuria has occurred.	Golomb, Evans 2008.
Serious adverse effects		
Rhabdomyolysis	The mean time of one year after statin initiation. Excess cases on cerivastatin.	Antons *et al.* 2006, Golomb, Evans 2008, Silva *et al.* 2006.
Pancreatitis	Lower risk of pancreatitis	Preiss *et al.* 2012, Wu *et al.* 2015.
	Increased risk of acute pancreatitis	Kuoppala *et al.* 2015.

A causal connection cannot be provided with epidemiological studies but only *ex post*, when the health impairment has already occurred in a significant fraction of the exposed population (Kundi 2006). The most important adverse effects are hepatotoxicity (Chalasani 2005) and muscle toxicity. Hepatic dysfunction is a risk factor for statin-induced myopathy because the predominant route of elimination for the majority of statins is via the bile after metabolism by the liver (Schachter 2005). An increase greater than threefold in incidences of transaminase is

approximately 1% for all statins and is dose related (Maron *et al.* 2000, Golomb, Evans 2008). A systematic overview of RCT's found statin therapy to be associated with a small excess risk of liver function test (LFT) elevations, but not of myalgias, creatine kinase (CK) elevations, rhabdomyolysis, or withdrawal of therapy compared with a placebo (Kashani *et al.* 2006). The proposed endogenous risk factors for statin-induced rhabdomyolysis include an age of over 80 years, renal and hepatic dysfunction, hypothyroidism, and hypertriglyceridemia (Antons *et al.* 2006) and exogenous, for example, alcohol consumption, heavy exercise, and drugs affecting the CYP3A4 mediated drug metabolism (Antons *et al.* 2006).

Variable incidence of muscle problems during statin therapy has been reported (Sirtori *et al.* 2012). They are rarely reported in randomised clinical trials but in clinical practice statin therapy has been associated with muscle problems in approximately 10% to 25% of patients (Bruckert *et al.* 2005, Cohen 2012). The true incidence is unknown and tests to confirm diagnosis are lacking. There are likely to be multiple and interactive mechanisms underlying statin myalgia (Taylor, Thompson 2015). Recent studies reveal that the effects of statins on muscle are largely nonspecific and not directly attributable to statin therapy (Taylor *et al.* 2015, Joy *et al.* 2014). These effects can occur with or without CK elevations, the vast majority of which are quite insignificant and may remain in the normal range. Actually, physical exercise may elevate CK much more than statins alone (Laaksonen 2013, Ballard *et al.* 2013). However, adverse muscle effects may reduce medication adherence and additionally physical activity and muscle strength. According to a systematic review of 42 clinical trials, the incidence of muscle effects in both statin and placebo groups was nearly identical and affected approximately 13% of participants (Ganga *et al.* 2014). A recent randomised, double-blind study of the effects of 80mg atorvastatin *vs*. placebo found no significant differences in muscle strength or exercise performance between the groups (Ballard *et al.* 2015).

In a recent systematic review of RCTs (14 primary prevention n=46 262 and 15 secondary prevention n=37 618 trials), only a small minority of the symptoms reported regarding statins was genuinely due to the statins; almost all reported symptoms occurred just as frequently when patients were administered a placebo. New-onset diabetes mellitus was the only potentially or actually symptomatic adverse effect with significantly higher rate for statins than the placebo (Finegold *et al.* 2014). Another meta-analysis of 13 randomised statin trials with 91 140 participants found statin therapy to be associated with a 9% increased risk for type 2 diabetes (OR 1.09, 95% CI 1.02–1.17) (Sattar *et al.* 2010) but interpreted the risk to be low both in absolute terms and when compared with the reduction in coronary events. Additionally, according to a recent Finnish population-based cohort-study (n=8749 men), participants on simvastatin or atorvastatin treatment had a 46% (OR 1.46, 95% CI 1.22–1.74) increased, dose dependent risk of type 2 diabetes after adjustment for confounding factors (Cederberg *et al.* 2015). A Canadian population based cohort study found an increased risk of incidences of diabetes when comparing the reference drug pravastatin with atorvastatin (adjusted HR 1.22, 95% CI 1.15–1.29), rosuvastatin (1.18, 1.10–1.26), and simvastatin (1.10, 1.04–1.17); this was regardless of their use for primary or secondary prevention of cardiovascular events (Carter *et al.* 2013). An Irish retrospective cohort study reported a 20% increase in the risk of type 2 diabetes associated with statin therapy. Increased risk of new onset treated diabetes was found with rosuvastatin (HR 1.42, 95% CI 1.33–1.52), atorvastatin (HR 1.25, 95% CI 1.21–1.28) and simvastatin (HR 1.14, 95% CI 1.06–1.23 (Zaharan *et al.* 2013). Several mechanisms for diabetogenic action of statins have been proposed; most have focused on increased insulin resistance or decreased insulin secretion (Brault *et al.* 2014). The clinical impact of diabetogenic risk as compared to the advantage of statin treatment is likely to be of minor importance. The benefits, such as the proportional reductions of 10% in all-cause mortality, 20% in deaths from coronary heart disease, and 22% in major vascular effects, far outweigh the

adverse effects in all but the very lowest risk individuals (Robinson 2015, Huupponen, Viikari 2013).

A meta-analysis of 16 placebo- and standard care-controlled statin trials with 113 800 participants has shown statin therapy to be associated with a lower risk of pancreatitis (Preiss *et al.* 2012). Similarly, a follow up study, with a median of 3.4 years, of a large retrospective cohort among nearly four million adult patients has shown the use of simvastatin and atorvastatin to be independently associated with a reduced risk of acute pancreatitis (Wu *et al.* 2015). However, one recent register-based case-control study showed an association between statin therapy and increased risk of acute pancreatitis. This association was more apparent during the first year of statin treatment and among former users (Kuoppala *et al.* 2015).

Simvastatin is administered as an inactive lactone prodrug, which undergoes extensive first-pass metabolism in the intestinal wall and the liver to simvastatin acid, the active metabolite of simvastatin (Pasanen *et al.* 2006, Neuvonen *et al.* 2006). Oxidative metabolism of simvastatin lactone in the liver is catalysed mainly by cytochrome P450 (CYP3A4). Active simvastatin acid is also metabolised mainly by CYP3A4. Genetic polymorphism in the SLCO1B1 gene, encoding the hepatic uptake transporter, the organic anion transporting polypeptide (1B1OATP1B1), markedly affects the plasma concentrations of simvastatin acid (Pasanen *et al.* 2006). Genetic variability in this polypeptide function can have clinically important consequences for the balance of risks and benefits of simvastatin treatment. Statins that undergo hepatic metabolism (simvastatin, atorvastatin, fluvastatin, lovastatin) are more prone to adverse effects than statins that are excreted mainly unchanged (rosuvastatin, pravastatin). Drugs that inhibit the CYP3A4 mediated drug metabolism (*e.g.* macrolide antibiotic) increase the exposure of many statins and the risk of statin adverse effects, and the pharmacokinetics is also affected by the genotype.

A placebo effect represents the benefits perceived by a patient arising solely from the appearance that a treatment is being delivered. This effect may be temporary or longstanding and the strength varies with the type of intervention (Olshansky 2007). A placebo can even appear to reduce the risk of death. A physician's advice, although an indirect form of intervention, can have powerful placebo or, unfortunately, nocebo effects.

A nocebo effect represents harm perceived by a patient arising solely from the appearance that treatment has been delivered. Repeat dosing increases nocebo effects and asking a patient about an adverse effect can increase nocebo effects. Women tend to report nocebo responses more than men (Olshansky 2007). Patients can create their own nocebo effect unwittingly. From the Framingham data, women with similar risk factors were four times more likely to die if they believed they were prone to heart disease (Voelker 1996). Nocebo and placebo responses may explain any therapy's true benefits and risks, and active therapies can have additional placebo and/or nocebo effects.

2.4.5 Clinical practice guidelines for treating dyslipidemia

The main aim with statin therapy is to lower the risk of CVD events. Dyslipidemia guidelines (Reiner *et al.* 2011, Anderson *et al.* 2013) base their recommendations on the total cardiovascular risk and emphasise promotion of a healthy lifestyle for cardiovascular disease prevention. Most guidelines use risk estimation systems based on, for example, the Framingham or the SCORE projects (Conroy *et al.* 2003, D'Agostino RB *et al.* 2008). In addition, current treatment guidelines highlight the importance of adherence to medication (Perk *et al.* 2012).

In principle, patients with known CVD, diabetes with microalbuminuria, very high levels of individual risk factors, or chronic kidney disease are automatically at high total cardiovascular risk and need active management of all risk factors. For all other people, the risk should be carefully evaluated by the clinician. In combination, several risk factors (gender, age, smoking, total cholesterol, LDL and HDL cholesterol, systolic blood pressure, family history, diabetes) may result in unexpectedly high levels of total CV risk, which may be higher than indicated among those with central obesity or diabetes. Similarly, among symptomatic individuals a family history of premature CVD may increase the total risk. Noteworthy, among young people with high levels of risk factors, a low absolute risk may conceal a very high relative risk requiring intensive lifestyle advice (Reiner *et al.* 2011). Conversely, high HDL cholesterol levels or a family history of longevity may decrease risk.

2.4.6 Utilisation of statins

In western societies, the utilisation of statins has markedly increased over the last two decades (Larsen 2001, Raymond *et al.* 2007, Mantel-Teeuwisse *et al.* 2002, Martikainen *et al.* 1996). Publication of the pioneering statin trials 4S (Scandinavian Simvastatin Survival Study Group 1994) and the three pravastatin studies; the WOSCOPS (Shepherd *et al.* 1995), the CARE (Sacks *et al.* 1996), and the LIPID (The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. 1998) boosted the incidence and prevalence of statin use. Table 7 illustrates the total number of patients receiving reimbursement for statins in Finland (see Appendix for a description of the Finnish drug reimbursement system). The share of these patients of the total population increased from 4% to 12% between 2000–2014. Recently, there has been a decline in the incidence of statin use. In Israel, for example, the incidence peaked in 2005 and halved by the year 2010 while the mean age at statin initiation decreased in both men and women from 59 years to 55 years between 2000–2010 (Shalev *et al.* 2014).

Table 7. The number of patients that have been eligible for the reimbursement of statins (ATC code C10AA) in Finland in 2000–2014, is based on The Finnish Medicines Agency Fimea and The Social Insurance Institution 2014.

Year	Number of patients receiving reimbursement (% of population)	Population of Finland
2000	216 428 (4%)	5 181 115
2002	305 305 (6%)	5 206 295
2004	414 939 (8%)	5 236 611
2006	509 288 (10%)	5 276 955
2008	610 913 (11%)	5 326 314
2010	680 611 (13%)	5 375 276
2012	663 195 (12%)	5 426 674
2014	655 439 (12%)	5 471 753

2.4.6.1 Adherence to statins

Despite the widespread and increasing use of statins (Ruokoniemi *et al.* 2008), the benefits of the medication in clinical care may be diluted due to suboptimal adherence (Mantel-Teeuwisse 2005). In practice, adherence to statins is suboptimal, the ability of the physicians to detect nonadherence is poor (Osterberg, Blaschke 2005), and as described before, several factors shape adherence behaviour. In a recent meta-analysis of 44 epidemiologic studies, the average

prevalence of nonadherence to statins, defined as taking less than 80% of the prescribed medication, was as high as 46% (Chowdhury *et al.* 2013). Table 8 shows factors reported to influence medication adherence according to their meta-analysis. At the end of two years, nonadherence can be as high as 75% (Brown, Bussell 2011). Moreover, in a Finnish study, one quarter of the new users discontinued statin therapy during the first year of treatment. In this nationwide register study, the discontinuation rate decreased within the next two years to an annual level of 1.5% and ten years after initiation, nearly 44% were still using statins (Helin-Salmivaara *et al.* 2008).

Patients with a history of cardiovascular events, hypertension, or diabetes have better adherence to statin therapy than individuals without these conditions (Mann *et al.* 2010, Helin-Salmivaara *et al.* 2010, Lemstra *et al.* 2012, Jackevicius 2002, Yang *et al.* 2003). Good adherence has also been associated with male gender and with an age of approximately 50–70 years (Chan *et al.* 2010). In addition, decreased costs enhance the continuity of statin use (Chee *et al.* 2014, Schneeweiss *et al.* 2007, Ellis *et al.* 2004). Expired patents and generic products have markedly lowered patients' co-payment of medication costs in many countries. In Finland, a generic substitution was introduced in April 2003.

Cholesterol target levels have decreased in the clinical guidelines (Stone *et al.* 2014, Reiner *et al.* 2011, Teeling *et al.* 2005) and statin use appears to be channelled towards healthier patients than previously (Teeling *et al.* 2005, Feely *et al.* 2000). Moreover, patients with good adherence tend to have healthier living habits. For example, they are more likely to seek for screening services or vaccinations, and they experience fewer motor vehicle or workplace accidents in comparison to those with poor adherence (Brookhart *et al.* 2007b, Dormuth *et al.* 2009).

Symptomatic patients and those with severe diseases (Li *et al.* 2012) may have better adherence than those on preventive medication for asymptomatic conditions, such as hypertension or dyslipidemia (Lemstra *et al.* 2012).

Table 8. Factors influencing medication adherence as reported in the statin studies, modified from Chowdhury *et al.* 2013.

Age	Gender	Social status	Mental illness	Co-morbidity	Poly-pharmacy	Cost or insurance cover	Name of the study (Author, year)
ns*	ns*			ns*	Yes		(Blackburn *et al.* 2005)
*	Yes*			Yes*	Yes		Lombardy-II (Corrao *et al.* 2011)
Yes*	Yes*	Yes*		Yes*	Yes	Yes*	Medstat MarketScan (Gibson *et al.* 2006)
Yes*	Yes*			ns	Yes		IDEAL (Holme *et al.* 2009)
ns	ns			ns			(Howell *et al.* 2004)
ns*	ns*			Yes*	Yes		JELIS (Origasa *et al.* 2010)
Yes*	Yes*				Yes*		PHARMO (Penning-van Beest *et al.* 2007)
Yes*	Yes*	Yes*	Yes	Yes*			RAMQ Med-Echo-I (Perreault *et al.* 2009a)
Yes*	Yes*		Yes*	Yes*	Yes*	Yes	Medco National Int (Pittman *et al.* 2011)
Yes*	Yes*			*			Emilia Romagna (Poluzzi *et al.* 2008)

Age	Gender	Social status	Mental illness	Co-morbidity	Poly-pharmacy	Cost or insurance cover	Name of the study (Author, year)
Yes*	Yes*		Yes	Yes*	Yes*	ns	InVision (Rublee *et al.* 2012)
Yes*	Yes*			Yes*	Yes*		(Ruokoniemi *et al.* 2011)
Yes*	ns*	*		*			MHS (Shalev *et al.* 2009)
Yes	ns	ns					MEMO-I (Wei *et al.* 2002)
Yes*	*			Yes*			LIPS (Lesaffre *et al.* 2003)

*Included in the multivariate model in the study
Yes = difference between adherence groups recorded; ns = not significant difference between adherence groups for this factor

2.4.6.2 Factors influencing prescribing

The effect of the expectations of patients for medications, and the perceptions of doctors of the patients' expectations when prescribing medicines, are generally strong predictors for the prescription (Himmel *et al.* 1997, Britten, Ukoumunne 1997). In a Swedish survey, statin users with only few CV risk factors tended to expect greater benefits from statins than those with several risk factors (Lytsy, Westerling 2007). A cohort study from 421 general practices in the United Kingdom found that the prescription of statins by general practitioners tended to be systematically influenced by cardiovascular risk factors—most strongly by older age, diabetic status, total cholesterol level, and a family history of premature coronary heart disease instead of a 20% or greater ten-year CVD risk, which is the threshold of the clinical guideline. Regardless of guidelines, this British study found cardiovascular risk was not the main predictor for prescribing statins (Wu *et al.* 2013). In addition to comorbidity, demographic factors, cost of medication, and their changes over time can affect the preferences for prescribing statins and explain selective prescribing. In Finland, restricting the reimbursement of expensive statins to patients who could not use cheaper ones increased the use of cheaper statins and expensive statins were channelled to patients with comorbidities (Martikainen *et al.* 2010). Similarly, channelling can also take place when a newly introduced drug is promoted as more potent than its predecessors. Finally, the experience of the physician may also contribute to decision to prescribe statins. Sir William Osler (1849–1919), a Canadian physician who has frequently been described as the "Father of Modern Medicine", has stated: *"The young physician starts life with 20 drugs for each disease, and the old physician ends life with one drug for 20 diseases".*

2.4.6.3 Discontinuation of statin therapy

In the process by which patients take their medications as prescribed, discontinuation marks the end of therapy (Vrijens *et al.* 2012). According to a Canadian meta-analysis of 67 studies, there are many factors known to be associated with discontinuation (Table 9) and different ways to define discontinuation: a 30 days gap in therapy, 6 months without taken out the prescription, failing to take out a new statin within 90 days, insufficient supply of drugs to cover less than 80% of the follow-up days, failure to renew medication for over 60 days and failure to renew medication for over four months (Lemstra *et al.* 2012). In addition, an over 270 days tablet-free gap between two consecutive prescriptions has been used (Helin-Salmivaara *et al.* 2010). Even though discontinuation is only a part of nonadherence, similar rates of statin nonadherence (56% based on PDC) and discontinuation (57%) has been observed among observational studies (Lemstra *et al.* 2012).

Table 9. Factors associated and not associated with discontinuation in previous statin studies, modified from Lemstra *et al.* 2012.

Retrospective cohort studies		
Factors associated with discontinuation	**Factors not associated with discontinuation**	**Country, population (study, year)**
Lack of follow-up with physician Lack of cholesterol testing No previous MI No other CV disease Non CV hospitalisation	Age Gender Initial statin Statin switching Previous CABG or PTCA DM	Canada n=239 911 (Brookhart *et al.* 2007a)
Age <45yr or >75 yr (*vs*. 45-75 yr) Gender, female No previous MI No HTN or HF No angina or IHD No CABG or PTCA	None	Italy n= 39 222 (Abraha *et al.* 2003)
Age (M,W) < 45yr Age (M) 45-49yr Age (M) 50-54yr No HTN (M,W) Hospital stay < 7 days (M) # hospitalisations previous year (M) Age (W) > 85yr	Other ages Cardiologist *vs*. GP Internist *vs*. GP # physician visits per year # other cardiac drugs #hospitalisations previous year (W) Hospital stay < 7 days (W) Year of study entry DM HF	Canada n=34 735 (Hudson *et al.* 2007)
No CAD Primary prevention No HTN No DM Gender, male Age, older # prescriptions (higher) # physician visits (lower) # physician visits (more)	CABG or PTCA	Canada n=143 505 (Jackevicius 2002)
No CHD	DM	US n=161 540 (Kamal-Bahl *et al.* 2007)
Not taking antihypertensive Not taking platelet inhibitors	Level of CV risk at start of follow-up	Netherlands n=59 094 (Penning-van Beest *et al.* 2007)
Gender, female Not living in a rural area No DM No HTN No respiratory conditions No anxiolytic agent use No antidepressant use # different drug classes/month(<3) # hospitalisations (1yr prior) Daily doses (≥3) # dispensing pharmacies (≥2) # prescribing physicians (≥3) # medical visits/month	Age Social assistance	Canada n=25 733 (Perreault *et al.* 2005b)

Statin used for primary prevention Age (younger) Gender, female No HTN No DM No anxiolytic agent use No antidepressant use Not living in a rural area # different drug classes (≤3) # daily doses (continuous) # pharmacies used (≥2) # prescribing physicians (≥3) # medical visits/month No hospitalisation (within 1yr)	Social assistance	Canada n=17 958 (Perreault *et al.* 2005a)
No enrolment in a cardiac rehab programme	Smoking Age Gender In-hospital revascularisation # co-morbidities # medications filled Year of MI DM	US n=292 (Shah *et al.* 2009)
Medication initiator Gender, female Age ≤65 *vs*. > 65yr Co-pay ≥US $36 *vs*. ≤ US $25 Annual income ≤ US $50 000 *vs*. > US $50 000	None reported	US n=818 165 (Vanelli *et al.* 2009)
Prospective cohort studies		
Factors associated with discontinuation	**Factors not associated with discontinuation**	**Country, population (study, year)**
HTN Primary prevention	Age Gender Country MI HF DM Cardiologists *vs*. non cardiologist Teaching hospital In-hospital events	14 countries n=6 320 (Eagle *et al.* 2004)
Non-institutional living Lack of a stroke care unit Self-perceived low mood Lack of follow-up A recurrent stroke Low self-perceived general health	Age Gender Satisfaction with hospital care Lack of support Type of stroke DM	Sweden n=7 275 (Glader *et al.* 2010)
Statin used for primary prevention Gender, female DM Smoking No prior CV adverse event Taking statin versus placebo	Age	US, Canada, Australia, New Zealand, Scotland n=9 802 (Pfeffer *et al.* 2002)

Randomised Controlled Trials		
Factors associated with discontinuation	**Factors not associated with discontinuation**	**Country, population (study, year)**
None	Age Gender Race	US n=10 355 (Margolis *et al.* 2009)
None reported	Adverse events	Europe n=4 444 (Pedersen *et al.* 1996)
Age > 65	None reported	Europe n= 5 129 (Tikkanen *et al.* 2009)

Abbreviations: CABG – coronary artery bypass grafting; **CAD** – coronary artery disease; **CHD** – coronary heart disease; **CV** – cardiovascular; **DM** – diabetes mellitus; **GP –** general practitioner; **HF –** heart failure; **HTN** – hypertension; **IHD** – ischemic heart disease**; M –** men; **MI** – myocardial infarction; **PTCA** – percutaneous transluminal coronary angioplasty; **W** – women; **yr** – year

Discontinuation, *i.e.* refraining from statin medication (Zhang *et al.* 2013) is regularly seen in both primary and secondary prevention groups (Ellis *et al.* 2004, Benner *et al.* 2002, Jackevicius 2002, Svensson *et al.* 2015). Within six months to one year after having been prescribed statins, approximately 25% to 50% of patients discontinue them (Brown, Bussell 2011). In the general population (in both primary and secondary prevention), the rate of discontinuation within the first year of prescription has been shown to be even 30% (Kamal-Bahl *et al.* 2007). The reasons for this decline in statin use are not entirely known but they are starting to be revealed (Table 10) (Svensson *et al.* 2015, Nielsen, Nordestgaard 2015, Upmeier *et al.* 2014, Ellis *et al.* 2004, McGinnis *et al.* 2007). In a recent, Danish nationwide prospective cohort study early statin discontinuation increased after negative statin-related news stories, while the opposite was true for positive statin-related news stories (Nielsen, Nordestgaard 2015). The same study found early statin discontinuation to be associated with increased risk of myocardial infarction and death from cardiovascular disease.

Table 10. Representative samples of previous studies on discontinuation of statin medication.

Population	Objective	Results	Author and study
A literature review of 58 studies	To evaluate patients' perceptions of statin therapy.	A major barrier to adherence was failure to appreciate the severity of potential complications. Other factors: lack of perceived benefits, perceived side effects, the cost of statins, poor physician-patient relationship, and overestimation of the effectiveness of diet control.	Chee *et al.* 2014.
Retrospective cohort utilising pharmacy claims and administrative databases. 2258 secondary and 2544 primary prevention patients	To compare statin nonadherence and discontinuation rates of primary and secondary prevention and to identify factors affecting suboptimal medication-taking behaviours. As regards discontinuation the analysis was restricted to statin-naive patients.	Primary prevention patients more likely to discontinue statin therapy relative to the secondary prevention cohort (relative risk 1.24; 95% CI, 1.08–1.43). Greater patient cost-sharing associated with a higher likelihood of discontinuing a statin.	Ellis *et al.* 2004.
Patients who discontinued cholesterol lowering therapy (n = 29) were interviewed within 18 months of hospitalisation	To explore clopidogrel and cholesterol-lowering therapy (CLT) discontinuance after an MI in order to understand patients' reasons for stopping these two medications.	The most common reason for CLT discontinuance was painful adverse effects, which interfered with daily life. Patients believed that they no longer needed therapy because their cholesterol had adjusted to an acceptable level.	Garavalia *et al.* 2009.
Retrospective cohort study based on administrative claims data. 490 024 new statin users	To analyse differences in the pattern of statin use among ten consecutive yearly cohorts of new users in Finland.	11% of statin initiators purchased only a single statin prescription. Increased CV risk or comorbidity, concurrent use of several CV medications, and the use of hormone therapy among women were positively associated with continuation of statin therapy.	Helin-Salmivaara *et al.* 2010.
A retrospective cohort study using administrative claims data for statins (n = 161 540)	To compare the discontinuation of newly initiated lipid modifying drugs classes in clinical practice in United States.	The median time to discontinuation was 27.5 months in the statin group. Adjusted cumulative incidence (95% CI) for statin discontinuation at 12 months: 28.9 (28.7–29.2), 18 months: 39.6 (39.3–40.0), and 24 months: 46.5 (46.1–46.9).	Kamal-Bahl *et al.* 2007.
Meta-analysis, 67 studies	To quantify the proportion of adherence to statin medications and to provide estimates of risk indicators associated with nonadherence to statin medications.	Six variables associated with nonadherence to statin medications: primary prevention (rate ratio 1.52; 95% CI 1.50-1.53), new statin users (1.46; 1.33-1.61), copayment (1.28; 1.09-1.50), lower income status (1.26; 1.16-1.37), and fewer than two lipid tests performed (1.38; 1.16-1.64), plus no hypertension (1.16; 1.12-1.21).	Lemstra *et al.* 2012.
Systematic review and meta-analysis of 22 articles on statin adherence predictors	To identify reliable predictors of non-adherence to statins.	Aged ≥ 70 years and < 50 years had lower adherence than 50–69 year olds. Women and those with lower incomes more likely to be non-adherent than men and those with higher income. A history of CV disease predicted better adherence to statins.	Mann *et al.* 2010.

Survey n=435	To examine the reasons why patients discontinue statins. To compare the patient and clinical factors of those who do and do not discontinue therapy.	Patient-reported reasons for discontinuing: adverse effects (42.2%), felt treatment unnecessary (14.0%), worry about adverse effects (12.7%), physician-advised discontinuation (8.5%), preferred diet and exercise (8.5%), felt they took too many medications (4.2%), or other (28.2%) (*e.g.*, did not want to take the drug for the rest of their life or ran out of renewals).	McGinnis *et al.* 2007.
All statin initiators in Denmark aged ≥40 in 1995-2010 (n=674 900)	To examine factors associated with statin discontinuation. To examine frequency and consequences of statin discontinuation.	Early statin discontinuation increased from 6% in 1995 to 18% in 2010. Factors increasing discontinuation were negative statin-related news (odds ratio 1.09; 95% CI 1.06–1.12), male gender (1.05; 1.03–1.06), and living in cities (1.13; 1.11–1.15). Positive statin-related news, baseline CV disease, and diabetes positively associated with continuation of statin therapy.	Nielsen, Nordestgaard 2015.
3 double-blind randomised trials	To assess efficacy and safety of pravastatin.	Factors increasing discontinuation of study medication: primary prevention, history of diabetes and smoking status.	Pfeffer *et al.* 2002.
Systematic literature search of 13 studies selected	The effects of statin non-adherence or discontinuation on cardiovascular and cerebrovascular outcomes.	Non-adherence in a primary prevention population was associated with a graded increase in CV risk. Individuals taking statins for secondary prevention were at particular risk when taking statin with highly variable adherence.	Phan *et al.* 2014.
Population-based data of 161 646 new statin users in Denmark	To examine the annual rate and cumulative prevalence of statin use including adherence of use and attainment of cholesterol targets.	Among the statin initiators, 26 314 (16%) completely stopped statin treatment. Compared with all patients, nonpersistent patients were more likely to be aged <45 or >75 years, live in small municipalities in rural areas, to be divorced, and have a slightly higher prevalence of almost all examined diagnoses of comorbidity, including CV disease.	Svensson *et al.* 2015.
All statin initiators in Finland aged ≥70 in 2000-2008 (n = 157 709)	To investigate patterns of statin treatment persistence.	76.9-80.5% persisted with statin treatment after one year. The probability to survive and remain persistent for four years was 51.6% and the probability to discontinue within the first year without restarting in the subsequent three years was 9.1%.	Upmeier *et al.* 2014.
A retrospective cohort study, a statin prescription between 1 Jan 2000 and 31 Dec 2008. (n=107 835)	To investigate the reasons for statin discontinuation and the role of statin-related events in routine care settings.	Statins were discontinued at least temporarily for 57 292 of the 107 835 patients. Reasons for discontinuation: no longer necessary, ineffective, adverse reaction, too expensive, rejected by patient, insurance cover, no prescription.	Zhang *et al.* 2013.

CI= confidence interval; CLT= cholesterol-lowering therapy; MI= myocardial infarction; CV= cardiovascular

2.4.7 Confounding in pharmacoepidemiological statin studies

A randomisation procedure eliminates the effect of systematic bias in controlled clinical trials (Schneeweiss 2006). However, real-world data is based instead on clinical consideration of the physicians, who take into account individual patient's risk as regards the outcome and the modifiable risk factors present, when making a decision to prescribe a medication. Therefore, when using real-world data, the measured and unmeasured confounding needs to be controlled or adjusted by a researcher with, for example, standardisation or multivariable regression (Schneeweiss 2006, Brookhart *et al.* 2010, Schneeweiss *et al.* 2012, Rubin 2007). A confounding variable, *i.e.* a confounder, is related both to the exposure and to the outcome of interest (Figure 6) and not in the causal pathway between exposure and outcome.

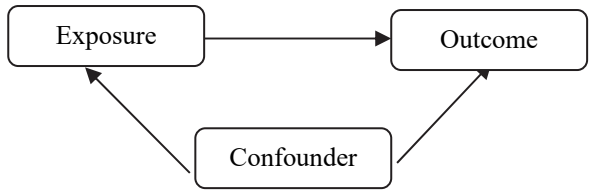

Figure 6. Counfounding. A confounder is related both to the exposure and to the outcome of interest.

For comparison, when one factor modifies the association between another factor and the outcome, the situation is called modification or interaction. For example, cardiovascular comorbidities can be considered as modifiers of the associations between lifestyle factors and nonadherence. Thus, the analyses should be done separately for respondents with and without cardiovascular comorbidities (Vandenbroucke *et al.* 2007).

Channelling is a form of allocation bias. It occurs when drugs with similar therapeutic indications are prescribed to groups with different prognostic factors. If channelling remains unrecognised or unmeasured, it may comprise an important source of bias. This possibility must be taken into account when designing pharmacoepidemiology studies. For example, when a newly introduced drug is promoted as more potent than its predecessors, channelling may lead to confounding by indication. This occurs because those who are prescribed this new drug may differ from those who are not prescribed it. For example, a drug may have contraindications and people with these conditions would all be in the non-exposed group. Thus, the exposed group may be healthier or younger. Additionally, a higher copayment for a new drug may channel it to a younger and healthier working population in comparison to pensioners. Similarly, in database studies unrecognised characteristics of patients (*e.g.* smoking, obesity) can increase unwanted events (*e.g.* pancreatitis) and this interaction may be misinterpreted as adverse effects.

Patients who adhere to preventive therapies (such as statins) may be more likely to have healthy lifestyle behaviour. Because many of these behaviours cannot be easily measured, observational studies of outcomes associated with the long-term use of preventive therapies are subject to the so-called healthy user bias or healthy user effect. A cohort study of 20 783 statin initiators between 1996–2004 observed, after adjustment for age, gender, and various comorbid conditions, that patients who purchased two or more prescriptions for a statin during a one year follow-up were more likely to receive prostate-specific antigen tests (HR 1.57, 95% CI

1.17–2.19), fecal occult blood tests (HR 1.31, 95% CI 1.12–1.53), screening mammograms (HR 1.22, 95% CI 1.09–1.38), influenza vaccinations (HR 1.21, 95% CI 1.12–1.31), and pneumococcal vaccinations (HR 1.46, 95% CI 1.17–1.83) than patients who purchased only one prescription during the follow-up (Brookhart *et al.* 2007b).

Immortal time bias is one form of information bias. It can occur in observational studies of medication effects under a variety of cohort designs (Suissa 2008). Immortal time refers to a period of follow-up during which death or the study outcome cannot occur, because of the study design. In pharmacoepidemiology studies, immortal time typically arises when the determination of a participant's treatment status involves a waiting period during which follow-up time is cumulated. For example, when a patient waits for a prescription to be dispensed after discharge from hospital, but the discharge date represents the start of the follow-up. This waiting period is considered *immortal* because individuals who ultimately are placed in the treated or exposed group have to be alive and event free until the treatment definition is fulfilled (Levesque *et al.* 2010). A recent Canadian study showed with a statin and diabetes progression example, that immortal time bias may be introduced by the use of a time fixed analysis in a cohort study; the immortal and untreated person-time was incorrectly allocated to the treated group in the time fixed analysis representing two thirds of the total follow-up for statin users. This resulted in a spuriously low rate of events for this group compared with that for non-users (Levesque *et al.* 2010).

2.4.8 Health behaviour and statins

Discretion of prescribing a statin involves assessment of the patient's lifestyle. The association between lifestyle factors (body mass index, smoking status, alcohol use and physical activity) and nonadherence would therefore be easily detectable and undemanding to utilise in improving adherence. Previous studies (Table 11) have found current smoking status (Pfeffer *et al.* 2002, Kopjar *et al.* 2003, Yang *et al.* 2003, Di Martino *et al.* 2005, Carey *et al.* 2012, Warren *et al.* 2013) and high alcohol consumption (Warren *et al.* 2013, Bryson *et al.* 2008) to be associated with nonadherence to statins. On the contrary, patients who reported regular exercise or a healthy diet had high scores of self-reported statin adherence in a primary care study (Natarajan *et al.* 2007). In addition, obesity has been linked with good adherence to statin therapy (Kopjar *et al.* 2003, Warren *et al.* 2013). However, some other studies found no association between adherence and obesity (Di Martino *et al.* 2005, Donnelly *et al.* 2008) or physical activity (Di Martino *et al.* 2005, Warren *et al.* 2013), and some even found an association between adherence to statins and smoking history (Donnelly *et al.* 2008).

Table 11. Representative samples of previous studies on lifestyle risk factors and adherence to statin therapy.

Population	Objective	Lifestyle risk factors	Other predictors/ confounders	Results (95% CI)	Comment	Study/ Country
5473 trial participants with and without CVD in 7 Veterans Affairs primary clinics, mean age 64 years	To identify whether alcohol misuse is associated with increased risk of nonadherece	Alcohol misuse (AUDIT-C score, incl. frequency and quantity of drinking and binge drinking) during the previous year prior to one year follow-up for adherence	Demographics: age, gender, race, marital status, education. Amount of medications, depression score	Fully adjusted proportions of adherence >80%: non-drinkers 66, low-level alcohol use 63, mild 63, moderate 58 and severe alcohol misuse 55; p=0.0001 for trend. Results for smoking not reported	In statin cohort: 22% current and 62% former smokers; 49% non-drinkers and 8% moderate or severe alcohol misusers	Bryson *et al*. 2008, USA
6673 patients with first MI aged 30-84 years, 5123 new and 1550 prevalent statin users, 2120 women, 4553 men	To examine trends in initiation and continuation of statin treatment after MI	Smoking status prior to MI (non, ex, current, not determined)	Age, gender, comorbidities	RR of continued statin for: ex 0.99 (0.97-1.02), current 0.96 (0.93-0.99) and undetermined 0.95 (0.90-1.01) smoking in comparison with non-smoking	Initial choice of statin had no effect on continued therapy, but social deprivation, older age and being a smoker were all associated with lower continuation rates	Carey *et al*. 2012, UK
4764 patients >30 years, mean age 59 years, 41% male	To estimate the factors associated with poor adherence to treatment	Body mass index, smoking habits, physical activity	Age, gender, diabetes, hypertension	Absence of atherosclerotic diseases, hypertension or diabetes and smoking were significantly associated with poor adherence. Smoker: risk of nonadherence OR 2.63 (1.06-6.55) *vs*. no smoker	Multivariable logistic regression adjusted also for physical activity and BMI, which were not significant in model	Di Martino *et al.* 2005, Italy
6462 statin initiators with diabetes, mean age 63 years, 48% male	To determine the patterns and predictors of long-term adherence to statin therapy, complete population-based information	Smoking history at initiation, body mass index	Demographics (age, gender), length of therapy, baseline glucose, comorbidities, concurrent medications, blood pressure	Predictors of nonadherence: younger age, higher blood glucose, no history of smoking, no CVD at baseline	A sharp decline in adherence in the first six months, followed by a more gradual decline over time. No association of statin adherence with statin dose. Maximum follow-up period >13 years	Donnelly *et al.* 2008, USA
8768 male Veterans Affairs members, 19.5% new users	To examine the persistence of using statins and characteristics with nonadherence	Smoking, obesity	Age, comorbidities, concurrent medications	Associated with nonadherence: current smoking odds ratio 1.25 (1.10–1.42), being new statin user 1.34 (1.19–1.51) and high diastolic blood pressure 1.33 (1.11–1.59) increases nonadherence, whereas obesity decreases 0.87 (0.81–0.94)	Logistic regression of new users showed only age >65 years associated with adherence	Kopjar *et al.* 2003, USA

284 patients aged ≥40 years, average 65 years, 57% men	To measure family practice patients' adherence to statins using a mailed self-report survey and to identify factors associated with adherence	Overweight, smoking status	Demographics, lifestyle (exercise ≥3 times a week and 3–5 servings of fruit/ vegetables a day), number of cardiovascular risk factors, beliefs and knowledge about cholesterol, comorbidities	Exercise and a healthy diet increases high adherence *vs*. no exercise and a non-healthy diet, odds ratio 3.14 (1.46–6.8). Patients >65 years are more than three times as likely to report high adherence as 40–54 year olds	90% of patients had drug insurance coverage, so the cost of medication was not a barrier. >60% of patients had been taking statins over two years, which may have affected adherence rates. According to previous studies patients' adherence to statins declines substantially in the first 1 to 2 years but then stabilises over time	Natarajan *et al.* 2007, Canada
19 592 patients, median age 59 years, 89% male, the mean exposure to statin medication 4.5 years	To evaluate potential safety issues and to estimate likelihood of discontinuing of statin	Smoking status	Age, gender, primary / secondary prevention, history of diabetes	History of diabetes, smoking and primary prevention predicted discontinuation. Hazards ratios for discontinuation: Smoking 1.25 (1.16–1.36), diabetes 1.34 (1.21–1.49), primary prevention 1.15 (1.04–1.26)	The WOSCOPS, the CARE, and the LIPID studies accumulated >112 000 person-years of exposure in double-blind randomised trials comparing placebo and pravastatin	Pfeffer *et al.* 2002
292 persons with MI, 75% (n=219) filled prescription for statins. 63% men, mean age 65 years. Long follow-up, mean 52±31 months.	To determine long-term adherence and factors associated with medication adherence with prescription claims database	Smoking	Age, gender, reperfusion/ revascularisation MI, comorbidities, family history	Cardiac rehabilitation was the sole independent predictor of improved adherence to statins (p=0.002): 80% of patients enrolled remained on statin *vs*. 61% who did not attend rehabilitation	78%, 59%, and 44% of statin users continued drug at 12-, 24-, and 36 months, respectively. Smoking was associated with increased likelihood of discontinuing though not statistically significant	Shah *et al*. 2009, USA
67 307 long-term statin users, age ≥45 years. 42 857 of them insurance card holders	To assess the factors influencing adherence in long-term medicational use of statins	Body mass index, smoking, alcohol use, physical activity	Age, gender, education, marital status, language, private insurance, employment status, income, self-rated health, previous heart disease, functional limitations, psychological distress	Participants >65 years, less healthy (worse self-rated health, pre-existing heart condition or obesity) or having private insurance had increased RR for adherence. Significant risk factors for nonadherence: being a smoker, being employed, reporting psychological distress	Response rate only 18%. Prevalent users. Large amount of missing data (44% missing data on some covariates).	Warren *et al.* 2013, Australia

22 408 LLD initiators (statin for 15 488) who received two or more recipes between 1 Jan 1990 and 31 Dec 1997	To evaluate the effects of comorbidities and patient characteristics among LLD initiators in a general population-based research database	Body mass index, smoking status, any history of alcohol /drug abuse	Age, gender, initiation year, coronary heart disease risks, concurrent medications, abnormal liver or renal function, comorbidities, number of general practice visits, psychiatric disorders	Current smoking decreased continuation: RR 0.85 (0.76-0.94) versus none smoking, past 1.06 (0.95-1.18). BMI 25–29.9 RR 1.07 (0.97-1.18), BMI≥30: 0.99 (0.88-1.12) versus BMI<25	The choice of LLDs, patient characteristics, comorbidities, and health care utilisation were associated with treatment continuation in patients newly treated with LLDs	Yang CC *et al.* 2003, UK

BMI= body mass index; **CI**= confidence interval; **CVD**= cardiovascular disease; **LLD**= lipid-lowering drug; **MI**= myocardial infarction; **OR**= odds ratio; **RR**= relative risk
WOSCOPS= The West of Scotland Coronary Prevention Study; CARE= the Cholesterol and Recurrent Events Study; LIPID= Long-term Intervention with Pravastatin in Ischemic Disease Study

2.5 Gaps in the evidence

Hypercholesterolemia is a common asymptomatic condition. Statins are one of the most widely studied and evidence-based medications (Taylor *et al.* 2013) and an essential component in treating hypercholesterolemia and thus, preventing cardiovascular diseases. Multiple patient, physician, and health system-related factors are known to affect medication prescribing patterns, adherence behaviour, and discontinuation of medical treatment—all of which may change over time. In real life populations, surprisingly little is known about the factors leading to nonadherence or discontinuation of statins and so more studies on identification of suboptimal statin use are needed.

The goals of this thesis are to address the prevalence of statin medication nonadherence and the predictors for nonadherence and discontinuation of statin therapy in real life populations.

3 AIMS OF THE STUDIES

The purpose of the studies in this thesis was to characterise the utilisation of statins and study predictors of statin adherence, nonadherence, and treatment discontinuation. The specific aims were:

1. To investigate preferential initiation with the two most frequently used statins, simvastatin and atorvastatin, by patient characteristics over time.

2. To investigate the associations between lifestyle factors and nonadherence to statin therapy among individuals with and without cardiovascular comorbidities.

3. To determine the patient characteristics that predict discontinuation of statin medication.

4. To examine whether retirement, a major life event, affects statin adherence among prevalent users.

4 MATERIALS AND METHODS

4.1 Subjects

The subjects included in the individual studies are described in Table 12.

Table 12. Study participants and statin prescription dates in the individual studies, in baseline.

Study	Date of the first statin prescription dispensed	Participants, n	Length of the statin-free period
I	Jan 1, 1998–Dec 31, 2004	408 394 initiators, total population, Finland	365 days
II	Jan 1, 1998–Dec 31, 2010	9285 initiators, FPS*	≥ 2 years
III	Jan 1, 1998–Dec 31, 2010	9285 initiators, FPS*	≥ 2 years
IV	Any statin prescription July 1, 2005–Dec 31, 2005	11 718 users, total population, Sweden	prevalent users

*FPS= Finnish Public Sector study

Study I included all statin initiators in Finland without a statin prescription during the 365 days preceding the initiation from 1 Jan 1998 to 31 Dec 2004. The individuals were identified by a unique social security number linked to each statin prescription. The prescriptions were captured from the nation-wide Prescription Register managed by the Social Insurance Institution of Finland (SII) and were further characterised using the corresponding anatomical therapeutic chemical (ATC) code assigned by the WHO (Table 4).

In 1998, statin therapy was initiated for 39 486 individuals in Finland (Table 13). During the follow-up, the number of individuals initiating statin therapy increased by 93% and included 76 300 individuals in 2004. In 1998, of the new statin users, atorvastatin was chosen for 18% (n=6 931) and simvastatin for 39% (n=15 487). In 2004, the corresponding figures were 32% (n=24 681) and 38% (n=29 006).

Table 13. Statin initiators in Finland, modified from Halava *et al.* 2009.

Year	New statin users	New users from 1 Jan 1998 to 31 Dec 2004 (% of all)			Without prior CV medication† (%)
		Atorvastatin	Simvastatin	Other statins*	
1998	39 486	6 931 (17.6)	15 487 (39.2)	17 068 (43.2)	10 374 (26.3)
1999	50 570	13 537 (26.8)	19 881 (39.3)	17 152 (33.9)	14 147 (28.0)
2000	58 842	17 283 (29.4)	22 351 (38.0)	19 208 (32.6)	17 804 (30.3)
2001	58 892	22 297 (37.9)	20 768 (35.2)	15 827 (26.9)	18 807 (31.9)
2002	60 789	21 650 (35.6)	27 367 (45.0)	11 772 (19.4)	19 453 (32.0)
2003	63 515	20 269 (31.9)	26 664 (42.0)	16 582 (26.1)	20 780 (32.7)
2004	76 300	24 681 (32.4)	29 006 (38.0)	22 613 (29.6)	26 639 (34.9)

*lovastatin, pravastatin, fluvastatin, cerivastatin, rosuvastatin

†cardiovascular (CV) medicines dispensed during the 365 days prior to the index date from the following classes: antithrombotics (ATC code B01), cardiac glycosides, antiarrhythmics and nitrates (C01), miscellaneous antihypertensives (C02), diuretics (C03), peripheral vasodilators (C04), beta-blocking agents (C07), calcium antagonists (C08) and agents acting on the renin-angiotensin system (C09)

The data for studies II and III were from the Finnish Public Sector Study (Vahtera *et al.* 2010), which included all local government employees from 10 selected towns and all employees in 21 public hospitals with a ≥6-month job contract in 1991–2005. Initially, in study II 80 459 participants responded to a survey in relation to demographic characteristics, lifestyle factors, and health status either in 1997–1998, 2000–2002, 2004, or 2008 (average response rate 70%). Using the unique personal identification numbers, data from national health registers (Furu *et al.* 2010),(Teppo *et al.* 1994) were linked to the survey data. The final study cohort of 9285 individuals who had initiated statin therapy after the survey, *i.e.* between 1 January 1998 and 31 December 2010, was identified among the respondents. Follow-up data for statin adherence was available until the 31 December 2011. In this study, an initiator was defined as a person who had not been dispensed any statins in the two years preceding the initiation (Table 12).

Restriction to statin initiators in studies I, II and III were used to facilitate comparability to previous studies, as the discontinuation rate for statin medication is the steepest within the first year after initiation (Lemstra *et al.* 2012). Within two years, the rate has been shown to decrease to an annual level of 1.5% (Helin-Salmivaara *et al.* 2008).

The data for Study IV came from the Insurance Medicine All-Sweden total population database (The National Social Insurance Agency). Initially, in this study, all individuals from 40–64 years of age (n=2 966 958) and living in Sweden on the 31 December 2004, were selected. From this population we included only those who took out a prescription for statins between 1 July and 31 December 2005 (n=222 665). Those who took out one or more statin prescriptions during the last six months of 2005, but had emigrated from Sweden or died by the 31 December 2010, or had retired or had no income from work in 2007 were excluded (n=12 010). Of the remaining individuals, all those granted a disability pension or retired in 2008, were selected. Thus, the final cohort comprised 11 718 statin users who had lived in Sweden between 2005 and 2010, were at work until 2007, retired in 2008, and for whom data was available on taking out statin prescriptions for the whole period of 2006–2010.

4.2 Study designs

Studies I, II and III was comprised of patients initiating statin medication. Study I is a population-based cohort study of 408 394 participants, based on the nation-wide Prescription Register of Finland in 1998–2004. In this study, the new users, identified for each year, were treated as distinct cohorts.

Participants in studies II and III were captured from the Finnish Public Sector Study (Laine *et al.* 2009). In these studies, participants had begun statin medication after completing a survey on demographic characteristics, lifestyle factors, and health status and had not been dispensed statins in the previous two years.

Study IV was a prospective study of all prevalent statin users in Sweden, who retired in 2008. This study utilises repeated measurements of statin prescriptions taken out two years before and after retirement.

4.3 Data sources

This thesis is based on four original cohort studies (Table 12). All the individual studies in this thesis used data from the administrative databases of drug reimbursement and health care systems, described in detail below.

4.3.1 Prescription Registers in Finland and in Sweden

In Finland and in Sweden, statins (ATC code C10AA) are available by prescription only. In Finland, the nation-wide Prescription Register is managed by the Social Insurance Institution (SII) of Finland (Furu *et al.* 2010). This register was introduced in 1994, and it includes, among other things, data on the dispensing date and the patient's birth date, gender, and residential area (The Finnish Medicines Agency Fimea and The Social Insurance Institution 2014). For each drug, the dispensing date, the ATC code (WHO Collaborating Centre for Drug Statistics 2011), and the quantity dispensed are recorded. The reimbursement system covers all permanent residents living in the country in non-institutional settings, and a unique identifing number is given to each person. During Study I, 1998–2004, the register coverage of the total statin consumption outside institutions ranged from 94 to 96% (Martikainen, J., the SII, personal communication). A part of these medications was directly funded by the employees' sick funds and prescriptions reimbursed by the local offices of the SII, instead of the direct reimbursement given by the chemist, and were therefore not recorded in the register. Over-the-counter (OTC) medicines are captured in the registry only when they are prescribed by a doctor (see Appendix).

In Sweden, The National Board of Health and Welfare provided data on statin use from the Swedish Prescribed Drug Registry. For each dispensed drug, information on the ATC code, the date of dispensation, and the quantity dispensed were available.

4.3.2 The Special Refund Entitlement Register of Finland

In Finland, patients with certain severe and chronic diseases are entitled to a higher rate of refund and are covered by a special register operated by the SII (see Appendix). The most common diseases generating payments under this category are chronic hypertension, diabetes, asthma, and coronary heart disease. This Special Refund Entitlement Register was first introduced in 1964 and it is managed by the SII (Furu *et al.* 2010). A patient's condition must meet explicit predefined criteria to be eligible for special reimbursements, and a written certificate from the treating physician is required. In 2014, the proportion of Finnish inhabitants receiving special reimbursement for medication costs was 22% (The Finnish Medicines Agency Fimea and The Social Insurance Institution 2014).

4.3.3 The National Social Insurance Agency of Sweden

The National Social Insurance Agency provided the starting date for the disability pensions. In Sweden, the ordinary retirement age is 65 years, but a pension can be taken earlier: all adults below the age of 65 years who have a permanently reduced work capacity due to disease or injury, can be granted a disability pension.

4.3.4 The Finnish Hospital Discharge Register and The Swedish patient register

The Finnish Hospital Discharge Register (FHDR) covers all Finnish hospitals and is managed by the National Institute for Health and Welfare. The FHDR was introduced in 1969 and it is one of the oldest nationwide, individual level, hospital discharge registers in the world (Sund 2012). It contains detailed data on discharge diagnoses and in-hospital procedures from 1994 onwards, in addition to clinical information on each day's surgical procedures, and, since 1998, information on outpatient hospital visits. Since 1996, the FHDR has used the 10th revision of the International Classification of Diseases (ICD-10) (WHO 2014). During recent years the reported coverage of the register has been above 95% (Sund 2012). The validity of the register for capturing CVD events is good: the sensitivity being 50–97%, but dependent on the diagnosis in question.

The Swedish National Board of Health and Welfare provided data from its patient register (dates and diagnoses according to the ICD-10) for hospitalisations and hospital-based out-patient care.

4.4 Measures of adherence

Adherence to statin use was investigated from various perspectives in Studies II, III, and IV. Standard follow-up periods of studies II, III and IV facilitated the assessment of adherence (Choo *et al.* 1999).

Adherence to statin therapy in studies II and IV was measured as PDC on the assumption of a daily dosage of one tablet. This method avoided double-counting of the prescription coverage. Statins are available in a range of different strengths, which enhances the possibility of applying a once-daily dosage regimen because the reported prevalence of prescribed daily dosages other than one tablet a day has been low (Lesen *et al.* 2011, Dormuth *et al.* 2008). Data including the date of dispensation, and the quantity dispensed for each dispensed drug, enabled the choice of PDC as a measure for adherence. Consistent with previous research, in studies II and IV nonadherence referred to a PDC of <80% (Chowdhury *et al.* 2013) and adherent use referred to a PDC of ≥80%. Although this conventional cut-off point 80% for dichotomy is somewhat arbitrary, it is the most widely used cut-off point for optimum adherence (Chowdhury *et al.* 2013) and was chosen to facilitate comparison with earlier studies. In Study III, statin initiators who took out only one prescription during the first year of statin treatment were defined as discontinuers. Long periods for defining discontinuation were chosen to avoid including short-term discontinuation with reinitiation as non-persistence. In Study IV, discontinuation was defined as no statin dispensations during a calendar year (Kildemoes *et al.* 2010).

4.5 Outcomes

In Study I, the outcome of interest was the choice of the most frequently used statins worldwide (atorvastatin or simvastatin) as initiators of statin therapy, with the purpose of investigating whether patient-related factors were associated with channelling.

Studies II, III, and IV focused on statin adherence and discontinuation. In Study II, the outcome of interest was nonadherence to statins during the first year after treatment initiation. The main analyses were conducted separately for those with and without cardiovascular comorbidities. The outcome of interest of Study III was the discontinuation of statin therapy during the first year of

treatment in participants who had not been dispensed any statins in the two years preceding the initiation. The primary outcome variable of Study IV was nonadherence to statins among patients who did not discontinue their therapy in the 5-year observation period, and centred on individuals receiving disability pension or retiring in 2008. The secondary outcome was the discontinuation of statin therapy.

4.6 Control for confounding

Study I was an analysis of multiple explanatory factors. In this study, several and equal explanatory factors were simultaneously placed in a logistic regression model to control for confounding.

In Study II, a logistic regression model was used to estimate the association between each lifestyle factor and nonadherence. The main analyses were stratified according to the patient's cardiovascular comorbidity status in order to control for confounding. This is because previous research has consistently shown that patients with a history of cardiovascular events, hypertension, or diabetes have better adherence to statin therapy than individuals free of these conditions (Mann *et al.* 2010, Lemstra *et al.* 2012, Latry *et al.* 2010). In a sensitivity analysis, a continuous PDC of prescriptions taken out was used as the outcome.

A logistic regression analysis was used in Study III to estimate the association of discontinuation with demographic characteristics, comorbidities, lifestyle factors, and co-payment. Only the respondents with complete data on all of the predictors were included. The first model was adjusted for the year of statin initiation. The significant predictors were then simultaneously entered into the second model to examine their independent effects on discontinuation.

To evaluate potential confounding in Study IV due to a change in the reimbursement regulations (in 2009), the trends in nonadherence between simvastatin and all statins were compared, since generic simvastatin also remained fully reimbursed under the new scheme (Pettersson *et al.* 2012).

4.7 Statistical methods

In Study I, binomial logistic regression analyses were performed to assess associations among the dichotomous outcome variable (atorvastatin *vs*. simvastatin), covariates (age, gender, socio-economic status, place of residence, coronary artery disease, hypertension, familial hypercholesterolemia, diabetes and the number of cardiovascular medicines), and year of initiation. The logistic regression analyses were performed in three steps. Firstly, all covariates were modelled separately. In this stage, the explanatory variables consisted of the covariate, the year, and an interactional term between the year and the covariate. Secondly, covariates were classified into demographic and disease-related subgroups. Covariates for these models were selected based on the results of the previous stage. The year was also included in these models, but the interactional terms was only included if they were statistically significant in the first stage. Thirdly, the subgroups were entered into a final model, where the explanatory variables consisted of the year and the significant covariates of the subgroups. Because many of the interactions between the year and the covariate were significant ($P<0.001$) in the subgroups, the final three-stage modelling was conducted separately for each year, using only the covariates as explanatory variables.

In Study II, a logistic regression model was used to estimate the association between each lifestyle factor and nonadherence. According to the aim of the study, the main analyses were done separately for respondents with and without cardiovascular comorbidities. These comorbidities were identified using linked data from special reimbursement claims (entitlements to special reimbursement for chronic hypertension, heart failure, coronary artery disease or diabetes) and hospital discharge registers (hospital admission for these conditions, stroke or arrhythmias during the 36 months before statin initiation). Each model was first adjusted for gender, age (24–50, 51–60, *vs*. 61–75 years), and, because of changes in prescribing practices and statin costs over time (Helin-Salmivaara *et al.* 2012), for the year of statin initiation. The final model was further adjusted for other confounders: education, marital status, residential region, suboptimal self-rated health, use of antidepressants, cancer, and similarly for other lifestyle factors. In this model, only respondents with complete data on all confounders were included. The associations between the number of lifestyle risks and nonadherence were analysed correspondingly. In Study III, a logistic regression model was used to estimate the association between demographic characteristics, comorbidities, lifestyle factors, and discontinuation of statin medication. The first model of this study was adjusted for the year of statin initiation and the final model was further adjusted for significant characteristics and significant lifestyle factors of the first model.

The analyses of study IV were based on a five-year observation period for medication adherence, including two years before and two years after the year of retirement. Data were stratified by gender and analyses were performed separately for those with at least one statin dispensation during a calendar year (continuers) and those with no dispensations (discontinuers). The annual prevalence of nonadherence and discontinuation was calculated by using a repeated-measures log-binomial regression with the generalised estimating equations (GEE) method to account for the intra-individual correlation between measurements.

4.8 Approvals

The protocol for Study I was approved by the SII as a part of a larger research project. Data management and data linkage in Study I was performed by the SII.

The protocol for Studies II and III was approved by the Ethics committee of the Hospital District of Helsinki and Uusimaa.

The regional Ethical Review Board of Stockholm, Sweden, approved Study IV.

Patient information was anonymised and de-identified prior to analysis. In all studies, the investigators received either unidentifiable patient data (Studies II-IV) or mere statistics (Study I). In none of the studies were patients contacted. Thus, in Finland, there was no legal requirement for ethics committee approvals. However, Studies II and III were approved by the Ethics committee of the Hospital District of Helsinki and Uusimaa, as part of a larger Finnish Public Sector Study research project.

5 RESULTS

5.1 Channelling of simvastatin and atorvastatin in Finland (Study I)

Statin therapy was initiated for 39 486 individuals in Finland in 1998 (Table 13). During the follow-up, the number of those initiating statin increased by 93% to 76 300 in 2004 (Halava *et al.* 2009). Atorvastatin was chosen for 18% (n=6931) of the new statin users in 1998 and simvastatin for 39% (n=15 487). In 2004, the corresponding figures were 32% (n=24 681) and 38% (n=29 006). The mean age of new users remained stable at 61.8 years over the study period. The share of people without prior CV medication increased to 35% from 26% over the period (Table 13). During study years 1998–2003, initiation with atorvastatin was less likely (ORs 0.62–0.73) for people with coronary artery disease (CAD) than for those without CAD (Figure 7) when compared to simvastatin, indicating a channelling of atorvastatin to individuals without CAD. Demographic factors and comorbidity affected the prescription preference for a particular statin at treatment initiation, and their impact changed over time. During the four years after its introduction, atorvastatin was channelled to people younger than 65 years of age and without CAD. This effect of age decreased during the follow-up and the differences in prescribing patterns between atorvastatin and simvastatin had almost disappeared by the end of the observation period in 2004.

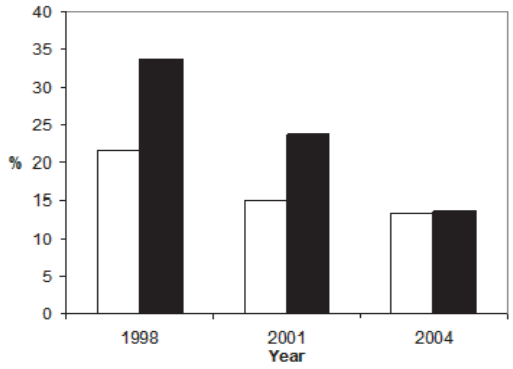

Figure 7.
Percentage of people with coronary artery disease among initiators prescribed with atorvastatin (blank) and simvastatin (black), adopted from Halava *et al.* 2009. Re-printed with the permission of the copyright owner.

5.2 Lifestyle factors as predictors of nonadherence to statins (Study II)

The association between lifestyle factors and nonadherence to statins varied according to cardiovascular comorbidity status (Halava *et al.* 2014). According to this study, the lifestyle factors of patients can help to predict whether or not they will follow the recommended statin therapy. Among new statin initiators without previous heart disease or diabetes, those who were overweight, obese or former smokers were more likely to adhere to statin therapy, since obesity (OR 0.86, 95% CI 0.74–0.99), overweight (OR 0.88, 95% CI 0.79–0.98) and former smoking (OR 0.82, 95% CI 0.74–0.92) predicted decreased odds of nonadherence (Table 14) in this subgroup.

Table 14. Nonadherence (PDC <80%) in statin initiators by lifestyle factors, based on Halava *et al.* 2014.

Lifestyle factor	Without (n=6458) cardiovascular comorbidities* OR (95% CI)	With (n=2827) cardiovascular comorbidities* OR (95% CI)
Body mass index		
<25	Ref	Ref
25–29.9	**0.88 (0.79–0.98)**	0.90 (0.74–1.09)
≥30	**0.86 (0.74–0.99)**	0.93 (0.76–1.14)
Smoking		
None	Ref	Ref
Former	**0.82 (0.74–0.92)**	0.97 (0.82–1.16)
Current	1.02 (0.88–1.18)	1.08 (0.86–1.35)
Mean alcohol consumption		
None	Ref	Ref
Moderate	1.10 (0.95–1.27)	1.10 (0.88–1.36)
High	1.11 (0.89–1.38)	**1.55 (1.12–2.15)**
Physical activity		
Active	Ref	Ref
Moderate	1.02 (0.91–1.15)	1.02 (0.84–1.24)
Low	1.01 (0.90–1.15)	1.00 (0.83–1.21)

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OR = odds ratio, CI = confidence interval, Ref = reference
*Cardiovascular comorbidities include hypertension, heart failure, coronary artery disease, diabetes, stroke, or arrhythmias.

Among the initiators with cardiovascular comorbidities, patients who had risky drinking behaviours or a cluster of lifestyle risks, were at increased risk of nonadherence: high mean consumption of alcohol (OR 1.55, 95% CI 1.12–2.15) (Table 14), extreme drinking occasions (OR 1.48, 95% CI 1.11–1.97), as well as clustering of 3–4 lifestyle risks (obesity, current smoking, low physical activity, risky alcohol use; OR 1.61, 95% CI 1.15–2.27) all predicted nonadherence. Further adjustment for other confounders and lifestyle factors changed these associations slightly. When compared with respondents not consuming alcohol, those with high alcohol consumption were 1.58 times more likely not to adhere (95% CI 1.11–2.25) and, compared with those without extreme drinking occasions, those reporting such occasions were 1.36 times more likely (95% CI 1.00–1.85) to become nonadherent. Finally, those with 3–4 lifestyle risks had 1.65 times higher odds of nonadherence (95% CI 1.16–2.34) compared with those with no such risks.

5.3 Predictors of first-year statin medication discontinuation (Study III)

Of the 9285 statin initiators, 88% continued medication and 12% (n=1142) discontinued it. Table 15 shows associations between baseline characteristics and lifestyle factors and statin discontinuation in this the study cohort. Older age, vascular comorbidity, and overweight or obesity were predictors of increased adherence to statin therapy: high age (OR 0.81, 95% CI 0.68–0.98), vascular comorbidity (OR 0.77, 95% CI 0.66–0.89), overweight (OR 0.83, 95% CI 0.71–0.96), and obesity (OR 0.75, 95% CI 0.63–0.90) were associated with decreased odds of discontinuation. In contrast, high patient co-payment of the first statin purchase (OR 1.32, 95%

CI 1.05–1.65) predicted increased odds of discontinuation. Additionally, among women but not in men, risky alcohol use was associated with increased risk of discontinuation.

The only significant difference between genders was observed for risky alcohol use. Among men, risky alcohol use predicted decreased odds of discontinuation (OR 0.66, 95% CI 0.47–0.92) whereas among women this behaviour-related risk increased discontinuation of statin (OR 1.32, 95% CI 1.05–1.66) (Table 15). Age and co-payment associated with discontinuation in women only and the corresponding association of obesity and former smoking were observed in men only but none of these gender differences were deemed significant.

The results from the fully adjusted model (adjusted for significant factors of the first model: age, comorbidity, co-payment, body mass index, smoking status, risky alcohol use, and the year of statin initiation) were substantially similar to the model adjusted for the year of statin initiation only. The difference between genders observed for risky alcohol use was almost unchanged (OR 0.69, 95% CI 0.49–0.98 in men and 1.28, 95% CI 1.02–1.62 in women).

Table 15. Association between baseline characteristics and lifestyle factors and statin discontinuation* among the 9285 initiators.

Characteristic	All n=9285 OR** (95% CI)	Male n=2211 OR** (95% CI)	Female n=7074 OR** (95% CI)
Gender			
Male	Ref	na	na
Female	1.01 (0.86–1.17)	na	na
Age group, yr			
24–50	Ref	Ref	Ref
51–60	0.85 (0.72–1.01)	0.95 (0.70–1.30)	**0.80 (0.66–0.97)**
61–75	**0.81 (0.68–0.98)**	1.03 (0.72–1.50)	**0.74 (0.59–0.92)**
Education			
High	Ref	Ref	Ref
Intermediate	0.88 (0.76–1.02)	0.85 (0.62–1.17)	0.89 (0.75–1.05)
Basic	1.03 (0.85–1.24)	1.24 (0.87–1.77)	0.96 (0.77–1.20)
Marital status			
Married	Ref	Ref	Ref
Single	1.00 (0.85–1.16)	0.90 (0.63–1.30)	1.02 (0.86–1.21)
Suboptimal self-rated health			
No	Ref	Ref	Ref
Yes	0.97 (0.85–1.11)	1.03 (0.79–1.35)	0.95 (0.82–1.11)
Use of antidepressants			
No	Ref	Ref	Ref
Yes	0.89 (0.75–1.06)	0.96 (0.63–1.46)	0.87 (0.72–1.06)
Cancer			
No	Ref	Ref	Ref
Yes	0.82 (0.49–1.39)	0.92 (0.32–2.61)	0.79 (0.43–1.45)
Vascular comorbidity†			
No	Ref	Ref	Ref
Yes	**0.77 (0.66–0.89)**	**0.66 (0.49–0.89)**	**0.81 (0.68–0.97)**
Copayment per first package			
low (<5 euros)	Ref	Ref	Ref

Characteristic	All n=9285 OR** (95% CI)	Male n=2211 OR** (95% CI)	Female n=7074 OR** (95% CI)
moderate (5–20 euros)	1.03 (0.87–1.23)	0.87 (0.60–1.24)	1.12 (0.92–1.36)
high (>20 euros)	**1.32 (1.05–1.65)**	1.02 (0.64–1.60)	**1.46 (1.12–1.90)**
Body mass index			
<25	Ref	Ref	Ref
25–29.9	**0.83 (0.71–0.96)**	0.80 (0.59–1.07)	**0.83 (0.70–0.98)**
≥30	**0.75 (0.63–0.90)**	**0.55 (0.36–0.83)**	0.83 (0.68–1.01)
Smoking status			
None	Ref	Ref	Ref
Former	0.88 (0.76–1.02)	**0.70 (0.51–0.96)**	0.93 (0.79–1.10)
Current	1.09 (0.91–1.31)	0.97 (0.68–1.37)	1.14 (0.92–1.41)
Risky alcohol user‡			
No	Ref	Ref	Ref
Yes	1.03 (0.85–1.25)	**0.66 (0.47–0.92)**	**1.32 (1.05–1.66)**
Physical activity			
Active	Ref	Ref	Ref
Moderate	0.87 (0.74–1.02)	0.92 (0.66–1.27)	0.85 (0.71–1.02)
Low	0.98 (0.84–1.15)	0.94 (0.68–1.30)	0.99 (0.83–1.19)

*Discontinuation=filled only one prescription during the first year of statin medication
OR = odds ratio, CI = confidence interval, Ref = reference, na= not applicable
** Odds ratios adjusted for the year of statin initiation.
† Hypertension, heart failure, coronary artery disease, diabetes, stroke or arrhythmias
‡ Risky alcohol user: mean alcohol consumption ≥16 drinks per week for women and ≥24 per week for men or passed out due to heavy alcohol consumption at least once during the 12 months

5.4 Influence of retirement on adherence to statins (Study IV)

Among the men, the prevalence of nonadherence remained at about the same level until the year of retirement, when adjusted for age at retirement (Halava *et al.* 2015). After retirement in 2008, there was a step-like increase from 17.7% in 2008 to 22.1% in 2010 in the prevalence of nonadherence (Figure 8A). This prevalence was 1.23 (95% CI 1.17–1.29) times higher in the two years after retirement when compared with the two years before retirement and observed in all of the subgroups. Between the subgroups, the only significant (P for interaction 0.048) difference in the relative increase in post-retirement nonadherence was observed for the prevention type: the prevalence ratio (PR) was 1.38 (95% CI 1.26–1.54) for secondary prevention and 1.18 (95% CI 1.13–1.25) for primary prevention.

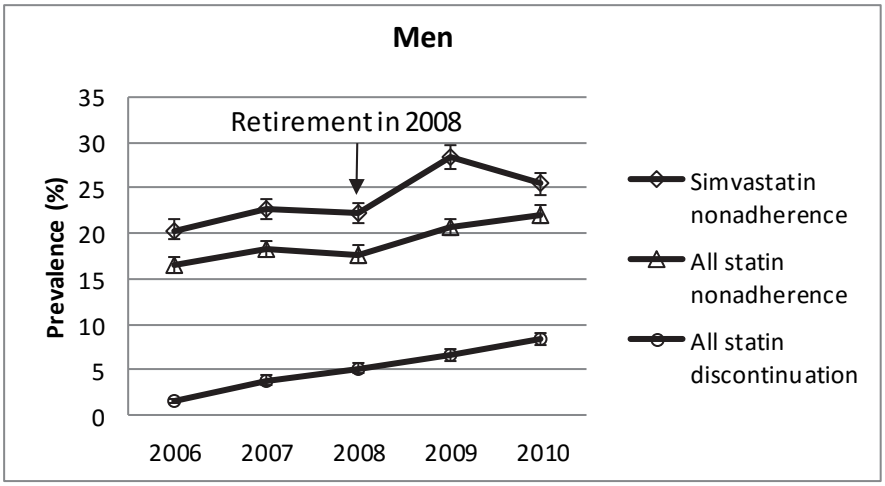

Figure 8A. Nonadherence and discontinuation prevalences in men, modified from Halava *et al.* 2015. Re-produced with the permission of the copyright owner.

Among the women, there was a similar, step-like increase in the nonadherence prevalence after retirement from 20.2% in 2008 to 25.1% in 2010 (Figure 8B). The PR for nonadherence after versus before retirement was 1.19 (95% CI 1.13-1.26) when adjusted for age at retirement. This significantly higher post-retirement nonadherence was observed for all the subgroups. Similarly as in men, the highest increase in the prevalence of nonadherence among the women was observed among those receiving statins for secondary prevention (PR 1.43, 95% CI 1.18–1.72); for primary prevention, the corresponding PR was 1.18 (1.11–1.24).

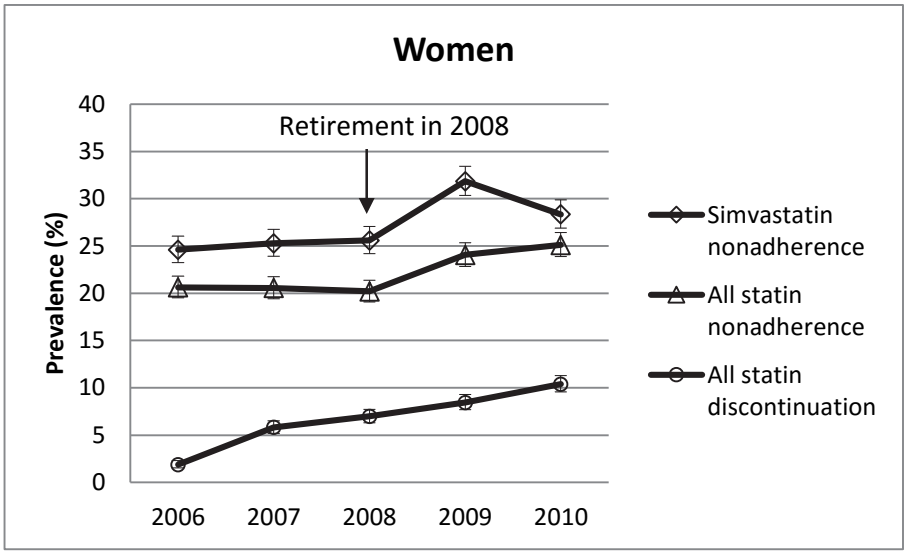

Figure 8B. Nonadherence and discontinuation prevalences in women, modified from Halava *et al.* 2015. Re-produced with the permission of the copyright owner.

6 DISCUSSION

6.1 General discussion

Register-based research is different from other quantitative research. While the register data have not been gathered for research purposes, these validated population-based registers contain a myriad of information collected by health care professionals. Data collection and utilisation is regulated by law to ensure patients' privacy and confidentiality.

Health care registers in general have a long tradition in Finland: a personal identification number system was introduced in 1964, and by 1968 all Finnish citizens and permanent residents had received their own number. Since then, practically all administrative registers have included this unique identification code (Gissler, Haukka 2004). This system of personal identification numbers permits data linkage of various registers and the collection of information on a personal-level.

The term 'multi-purpose database' was defined as a healthcare database that was collected for other purposes but used in observational research (Hall *et al.* 2012). This includes electronic medical records, healthcare claims for reimbursement or payment records, but is not limited to them. In Finland, many register keepers, such as the Social Insurance Institution of Finland and the National Institute for Health and Welfare, maintain nationwide health registers for administrative and statistical purposes. The advantages of these databases are the limitation of recall and reporting bias, lower costs, rapid data gathering, and the representativeness for large populations (Hall *et al.* 2012, Schneeweiss, Avorn 2005). The disadvantages with these multi-purpose databases include the limited number of variables, the difficulty of extending these data collections to include new variables or illustrate causality. Additionally, information, for example, on lifestyle factors is limited.

One of the main preconditions for the utilisation of register data is good quality. The data has to be in accordance with reality and all events need to be included in the database. This eliminates the possibility of selection and recall bias. Immortal time bias can be avoided by choosing the dispensing date of the first prescription as the index date.

In other words, a register needs to have good coverage and validity. Several Finnish administrative registers have been shown to qualify for this requirement both in studies that compare the internal validity of a register (Gissler, Shelley 2002) and in studies comparing register data with information from the primary source (Teppo *et al.* 1994, Isohanni *et al.* 1997). Therefore, in Finland, as in the other Nordic countries, there are significant possibilities for research because of this reliable, population-based register data.

Patients come to the physician with their own beliefs and experiences. Lifelong medical treatment requires commitment and persistence, which may be more difficult to implement with symptomless conditions or with medications thought to have adverse effects. The problem is that adverse effects are concrete but total benefit on a personal-level is based on probabilities. Following the medical examination, the physician may recommend a prescription. As in any medical therapy, but especially in relation to preventive medication, the pros and cons must be considered carefully. The decision to prescribe the medicine may be made solely by the health professional or through a discussion between the health professional and patient. After

receiving a prescription patients may or may not take out the prescription prescribed. Even if the medicine is dispensed, they may or may not take the medicine (National Collaborating Centre for Primary Care (UK) 2009).

After receiving and redeeming a prescribed statin therapy, the medications may then be discontinued for many reasons. Most patients are not prepared to take medication every day for their lifetime. In a British meta-analysis of 376 162 patients (mean age 64 years, 49% male) an overall summary of adherence to cardiovascular drugs was 57% (95% CI 50–64) over a median treatment period of 24 months. Adherence was 50% (95% CI 45–56) in primary and 66% (95% CI 56–75) in secondary prevention studies. This was similar for all classes of drugs, indicating that side effects are not the main cause of low adherence (Naderi *et al.* 2012).

Adherence needs to be improved to achieve the best benefit and everyday effectiveness of statin therapy since the potential preventive effect of medications is reduced when patients stop taking a treatment that is intended to be taken for life or take it less regularly, or in lower doses than prescribed. Any attempts to improve adherence must involve the patient in the decision-making process.

The options for lowering cholesterol levels may increase in the future. Two novel cholesterol-lowering medications, alirocumab and evolocumab, have been shown to cause large reductions in LDL cholesterol levels (Nissen *et al.* 2016). Among patients with statin intolerance, the use of these novel medications could be advantageous, since the mechanism of action differs from statins. These fully humanised monoclonal antibodies inactivate proprotein convertase subtilisin-kexin type 9 (PCSK9). This inactivation results in decreased LDL-receptor degradation, increased recirculation of the receptor to the surface of hepatocytes, and a consequent lowering of LDL in the bloodstream (Everett *et al.* 2015). Both PCSK9 inhibitors cause large reductions in LDL cholesterol levels, as compared with a placebo (39–62% reduction for alirocumab and 47–56% for evolocumab). However, definitive evidence of reduced cardiovascular event rates is yet unproven (Everett *et al.* 2015).

6.2 Principal findings

Demographic factors and co-morbidity affected the prescription of statins and their impact changed over time. Atorvastatin channelled to patients younger than 65 years and those without coronary artery disease during the four years after its introduction. The effect of age decreased during the follow-up and the differences between atorvastatin and simvastatin almost disappeared by the end of the observation in 2004. Since atorvastatin was promoted as a potent statin (Jones *et al.* 1998), it was assumed to have been preferred for secondary prevention patients. However, the opposite was found which may have affected the treatment outcomes in public health level. Medical treatment is cost-effective when low-priced drugs are used whenever they are potent enough to produce the benefits expected. The younger and wealthier patients tended to receive a potentially more effective atorvastatin, possibly partly because they expected greater benefits from statins (Lytsy, Westerling 2007); it is, however, conceivable that the money spent on these statins could have been used in a more cost-effective way. The observed influence of residential region may reflect different marketing efforts, but also differences in patient demography in different parts of Finland. Cost is an unlikely explanation for the channelling because the prices of simvastatin and atorvastatin were at the same level until 2003 (Table 16).

Table 16. The prices of 98 or 100 tablet packages of simvastatin and atorvastatin in Finland in 1998–2016.

Year*	Brand name atorvastatin Lipitor® 10mg†	Brand name simvastatin Zocor® 20mg†	Generic atorvastatin 10mg†	Generic simvastatin 20mg†
1998	129.15	183.44	na	na
1999	117.65	163.54	na	na
2000	117.65	163.54	na	na
2001	117.65	163.54	na	na
2002	117.65	163.54	na	na
2003	117.64	163.54	na	114.47
2004	117.64	163.54	na	53.33
2005	117.64	48.99	na	25.44
2006	117.64	48.99	na	14.17
2007	112.08	46.61	na	9.00
2008	110.51	46.61	na	8.87
2009	110.51	46.61	na	6.86
2010	64.00	46.61	25.70	5.50
2011	64.59	47.04	14.20	4.80
2012	64.59	47.04	16.43	6.20
2013	64.59	47.04	22.40	12.15
2014	65.19	47.48	27.02	16.74
2015	66.99	45.28	28.44	21.60
2016	66.99	45.28	34.41	27.54

*To allow between year comparisons, the price of statins in Finnish marks in 1998–2001 were converted to euros by dividing with an exchange rate of 5.94573.
†For equivalence atorvastatin 10mg=simvastatin 20mg (Weng *et al.* 2010)
na= not applicable

The association between lifestyle factors and nonadherence to statin therapy varied according to the cardiovascular comorbidity status. These findings are in agreement with previous studies demonstrating that patients in secondary prevention have better adherence to statin therapy than patients in primary prevention (Mann *et al.* 2010, Lemstra *et al.* 2012, Latry *et al.* 2010). Patients with comorbidities are more likely to have an accurate understanding of the need for statin treatment (Berglund *et al.* 2013) because of their increased risk of cardiovascular events (Reiner *et al.* 2011). Information on lifestyle factors was only helpful in predicting the risk of nonadherence among people with cardiovascular comorbidities. In this group, risky drinking behaviours or a cluster of lifestyle risks predicted increased risk of nonadherence. Among those without cardiovascular comorbidities, lifestyle factors were unhelpful in identifying factors associated with increased risk of nonadherence, but those who were obese, overweight, or former smokers had better adherence than those without these lifestyle factors. Moreover, overweight and obese patients, and smokers have an increased cardiovascular risk. Thus, a greater clinical need for statin therapy may also have strengthened their motivation to adhere to medication (Berglund *et al.* 2013, Mann *et al.* 2007).

Retirement was found to increase statin nonadherence and what is disconcerting is that this increase was highest among those having statin for secondary prevention. The reasons for the observed increase in post-retirement nonadherence are not known. It is possible that the removal of exposure to adverse work situations or positive changes in lifestyle may improve the

individual's perceived health condition after retirement (Westerlund *et al.* 2009) and thus, impair motivation to adhere to preventive medication. To promote adherence, the health care system should ensure that the patient contacts a primary care physician after leaving an occupational health care system. The change in daily routines after retirement could explain temporary nonadherence but the level of adherence did not return to the prior level even during the second year of retirement. Previous studies have found major life changes to associate with a lower adherence to medication (Krousel-Wood *et al.* 2011). However, retirement is rated as being one of the least severe life events (Vahtera *et al.* 2007).

Many patients for whom statins are prescribed discontinue the drug within a year, which is likely to reduce any benefit from the medication and increase the risk of cardiovascular events (Jasinska-Stroschein *et al.* 2011, Phan *et al.* 2014). In this study, some predictors of discontinuation were found to help identify those with an increased risk of nonadherence. Among the women, risky alcohol use was associated with an increased rate of statin discontinuation in primary prevention and it was a result of binge drinking, not high average consumption of alcohol. Thus, it is important to ask about and recognise this lifestyle risk, and women themselves need to be more aware of their own risk factors. Previous research has shown that the prevalence of MI has increased in midlife (35–54 years) women over the last decades, while declining in similarly aged men (Towfighi *et al.* 2009). Cardiovascular disease is the major cause of death in women and is still under-recognised and undertreated (Maas, Appelman 2010).

Additionally, a high level of patient co-payment was an independent factor for increased statin discontinuation. Thus, unnecessary statin-related costs should be avoided to achieve adherence and improve treatment outcomes and results in public health.

6.3 Strengths and limitations

These longitudinal studies based partly on the register data and partly linked to questionnaires involving demographic characteristics, lifestyle factors, and health status, have a number of strengths.

Firstly, one strength of using the prescription data is that all dispensed prescriptions of statins in the entire population were used, which eliminates the possibility of selection and recall bias. Due to the universal drug reimbursement system in Finland and in Sweden and the availability of statins by prescription only, the Prescription Registers provided comprehensive and valid data on statin purchases. In addition, there was a possibility to analyse the impact of various patient-related factors potentially explaining initiation with a distinct statin. Secondly, these studies used the new-user design, which, due to the complexity of identifying new users of medications, is rarely used for pharmacoepidemiologic studies (Ray 2003). This design differs from most observational studies in that it excludes prevalent users and enables the instigation of the study follow-up to be synchronised with the initiation of the medication. This design avoids susceptibility to biases related to underestimation of adverse effects occurring early in therapy and the modification of variables on the causal pathway (Ray 2003).

In spite of these strengths, register based studies have some limitations as well. As with any pharmacy claim database study, it can only be determined that a prescription was taken out, not that a patient actually took the medicine (Suissa 2007). Moreover, the prescription register information was used to estimate actual pill intake. Only the data for reimbursed drug purchases

was available and therefore, no data could be supplied on statins prescribed but not purhased. This excludes primary discontinuers, who never take out the first prescription. There was no opportunity to update the prescription data to the present situation either, since the data is not available. This would have required a completely new permission and data collection of the new statin initiators.

An important strength of the cohort studies II and III is that they contained detailed health status information and lifestyle factors rarely interrelating with prescription claims databases. Additionally, all these studies had a large sample size with excellent follow-up. Secondly, the generalisability of these findings is expected to be greater than in clinical trials as these studies involved cohorts of unselected statin users (both men and women) in real-world practice. Thirdly, separate analyses (II) according to cardiovascular comorbidities prior to statin initiation were conducted to avoid confounding, as these comorbidities have shown to both predict better adherence to statin therapy (Helin-Salmivaara *et al.* 2008, Mann *et al.* 2010, Lemstra *et al.* 2012) and to associate with an increased risk for future CVD events.

However, due to the specific target population (public sector employees, for the most part nurses and teachers), the external validity of studies II and III is limited and these results are not generalisible to the entire population or other populations. Second, it is possible that those with the unhealthiest lifestyle and highest rates of nonadherence are less likely to participate in a study than people with a healthier lifestyle. A major bias due to internal validity, selection or missing data, appears unlikely since the risk of nonadherence was only five percentage points larger among the non-respondents than the respondents. Third, as the study was an analysis of all statins instead of an examination of individual statins, possible differences in adherence or discontinuation between individual statins could not be determined. Fourth, the performance related factors of the health care systems and physician were not available, although they associate with adherence and discontinuation (Sabaté 2003, Osterberg, Blaschke 2005). Fifth, self-reporting tends to underestimate obesity and overweight (Wills *et al.* 2011) as well as smoking and alcohol use (Fendrich *et al.* 2005, Ekholm *et al.* 2011). This selective underreporting of lifestyle risks could result in misclassification. This bias in non-adherent users can not be entirely excluded and can possibly underestimate the effects of these lifestyle risks. Sixth, there was no information on the reasons for discontinuation of statin therapy or of drug-related adverse effects, such as muscle effects, CK or LFT elevation, or diabetogenic effect, which may have affected adherence or discontinuation of statins. However, in the WOSCOPS, adverse effects accounted for only 2% of discontinuations, with the overall discontinuation rate of 30% at five years (The West of Scotland Coronary Prevention Study Group 1997). Furthermore, in a retrospective cohort study of 107 835 patients more than half of the study patients discontinued their statin, but only 3.9% of them reported an adverse reaction as the reason for the discontinuation (Zhang *et al.* 2013). Seventh, there were no data on cholesterol concentrations, family history, or assessment of the patient's total cardiovascular risk, which may have affected the perceived need for adherence to or discontinuation of the statin therapy.

Finally, in Study IV, conditioning on survival leads to immortal time. The participants had to survive until two years after retirement since this data was needed for reliable comparison of adherence before and after retirement in 2008. This period of follow-up, during which death was not possible (*i.e.* the period between cohort entry and the end of the follow-up), was immortal. However, we used a repeated measurement approach for analysis, and there was no misclassification of person-time that could lead to an immortal time bias. Excluding those who died could lead to misconception of a more healthy population, and thus the results may not be

representative of all those who retire. Only a small percentage (5%) of the participants died or migrated before the end of the follow-up. Thus, a major selection bias seems unlikely.

6.4 Adherence to statin therapy

To improve adherence, patients need to be given the opportunity to tell their story and to present their point of view to the physician (Martin *et al.* 2005), *i.e.* to offer a good patient-provider relationship. The physician needs to perceive cognitive factors, memory, and the ability of the patient to follow directions. Possible solutions, reminders, and a support network, should be used on demand. Moreover, simple regimens, lower out-of-pocket costs, and adequate health care coverage promotes adherence.

In Finland, in public healthcare, the electronic prescription system is already in use in all pharmacies, and also used by most of the private sector. Only healthcare units issuing fewer than 5000 prescriptions a year, self-employed practitioners, social service providers, and units in the Åland Islands may still use paper prescriptions but they must adopt the electronic prescription system by 31 December 2016. In the future, electronic monitoring, mobile health strategies, or reminders could enhance patient adherence to prescribed medicines (Vrijens *et al.* 2006).

Medicines, especially statins, are widely used not only to cure conditions but to prevent ill health in the future. In a complex medicine-taking behaviour patients evaluate the risks and benefits of medicines using the source materials available to them. Unwanted and unused medicines reflect insufficient communication, reasoning, and comprehension between a provider and a patient.

In the real world, cost-effectiveness of medical treatments is worse than expected based on RCT's. In addition, the cost-effectiveness of statin therapy in primary prevention depends not only on the cost of the drugs themselves but also on the patients' CVD risk level. The absolute benefit is greater in patients with a high risk for CVD (Greving *et al.* 2011). For example, even though generic statins are now low-cost drugs in Finland, treatment adherence seems to have a major impact on the cost-effectiveness of statin treatment in primary prevention. Better adherence has been reported to be associated with lower overall health care costs (Aarnio *et al.* 2015, Bitton *et al.* 2013). To obtain the full benefit of the investment in statins, improving adherence is of major importance (Aarnio *et al.* 2015).

Different guidelines and risk scores can lead to divergent interpretations of treatment decisions (Kavousi *et al.* 2014). Furthermore, the costs of illness differ between countries. In addition to the direct costs of statins, they should ideally include factors that are more difficult to measure, such as morbidity (hospitalisation, outpatient care, laboratory tests), work-related costs (sickness leaves due to CVD events), and rehabilitation. In the United States, researchers have recently suggested that it would be cost-effective to treat even 48-67% of all adults aged 45-75 years with statins. According to their study, a shifting from the current treatment guidelines (7.5% or higher total atherosclerotic cardiovascular disease risk threshold) to the 3.0% or higher risk threshold might be justifiable on cost-effectiveness grounds even accounting for side-effects (Pandya *et al.* 2015).

Recent wireless technologies have provided a new way to connect with patients at relevant times. In the future, new payment approaches may influence a physician's income as regards

achieving population health outcomes. A trial in the United States has recently shown that in primary care practices, shared incentive payments for physicians and patients, but not incentives to physicians or patients alone, resulted in a statistically significant difference in reduction of LDL cholesterol levels at 12 months (Asch *et al.* 2015). This reduction was modest, but provides insight into various mechanisms for adherence with preventive medication, such as statins.

As a consequence, further effort is needed to motivate patients' adherence to treatment, especially in risk groups, in order to reduce nonadherence and discontinuation and thus, cardiovascular events. Undoubtedly, there is also a possibility of overtreatment, particularly among primary prevention patients with moderately increased CV risk. Nevertheless, this issue is outside the scope of this thesis and for the most part avoidable with medications based on the total cardiovascular risk evaluation.

7 CONCLUSIONS AND IMPLICATIONS

The aim of the studies in this thesis was to describe prescribing patterns and utilisation of statins. In Finland, statins are widely used: of the population 12% (n= 661 200) were eligible for reimbursement for statins in 2015. Prescribing statins is affected by co-morbidity but also other factors, such as demographics, may contribute to the prescription of the drug. The patterns of prescribing have changed over time. Recognising the reasons behind these patterns is of primary importance in understanding why evidence based clinical guidelines has not translated into prescription behaviour.

Atorvastatin was seen to have been channelled to those without coronary artery disease even though atorvastatin was promoted as a potent statin and assumed to have been preferred for secondary prevention patients. In addition, the adoption of statins differed between medical specialities and regions of residence, which may reflect different marketing efforts between specialities or regions. This channelling may have affected the treatment outcomes at the public health level. It is possible that money spent on statins in Finland in 1998–2004 could have been used in a more cost-effective way.

Cardiovascular comorbidity status affected the association between lifestyle factors and nonadherence to statins. It is noteworthy and disconcerting that among new statin users with previous cardiovascular comorbidities those with risky drinking behaviours or a cluster of lifestyle risks were at an increased risk of nonadherence. Emphasising the importance of adherence is essential, especially among patients with these lifestyle risks.

High patient co-payment and risky alcohol use in women predicted the discontinuation of statin therapy. To reduce the rates of statin discontinuation, the instructions should be tailored to the patient's lifestyle and needs, and thus, to commit the patient to the medical therapy. Furthermore, the selection of cheaper alternatives could decrease discontinuation.

The prevalence of nonadherence to statins increased after retirement among men and women in all subgroups. The highest increase was found among those receiving statins for secondary prevention. This finding is significant because the proportion of people aged 60 years or older is growing rapidly and the need for statins is highest among secondary prevention patients. Recognising this post-retirement risk is important because nonadherence to statins is associated with an increased risk of adverse cardiovascular outcomes and higher healthcare costs. Increasing adherence to medications and a healthy lifestyle could slow the processes of the most common old age disorders, such as ischaemic heart disease (Jagger *et al.* 2008).

The lack of adherence found in the studies in this thesis indicates that the effectiveness of statins in clinical practice may be worse than expected on the grounds of the efficacy introduced in RCTs. Despite the proven benefits, the low cost, and few adverse affects, effectiveness is limited, when even half of the patients who are prescribed statins, discontinue them within a year (Maningat *et al*. 2013, Brown, Bussell 2011).

The findings of this thesis can have several clinical implications. A considerable proportion of the population in western societies use vitamins, supplements, and trace elements without asking for, and indeed in spite of physicians' opinions. Money spent on these expensive and unproved therapies might be better spent on evidence-based medicine. Recommending widely studied, well tolerated, safe, and inexpensive statins to patients with a risk of cardiovascular

disease is a physician's duty as a heath care provider. To reach the optimal effectiveness of statins, physicians should optimise their patients' understanding of the benefits of the medication and involve them in the treatment.

In statin-intolerant patients, the use of PCSK9 inhibitors could be an alternative, however, statin intolerance appears to be overdiagnosed (70% of patients considered unable to take statins tolerated 20 mg of atorvastatin daily for 24 weeks) (Everett *et al.* 2015). In addition, the evidence of the clinical benefit of statins is more persuasive. Furthermore, alirocumab and evolocumab are both given by injection, and their price is substantially higher than statins. In the US in 2015, evolocumab (*Repatha*) cost $14 100 and alirocumab (*Praluent*) $14 600, for a year's prescription. In Finland, both PCSK9 inhibitors cost roughly €7 800 per year. Consequently, the effects of these factors on adherence are not known. Among statin users, in the absence of any reliable evidence of adverse effects or lack of efficacy, adherence to statin medication could be required as a prerequisite, prior to prescribing a PCSK9 inhibitor.

Providers should develop a good relationship with patients to make sure that they understand how lifestyle affects cardiovascular disease risk. This lifestyle modification in cardiovascular disease prevention is underutilised. Mobile health strategies could help to address this gap. In an Australian RCT, the use of a lifestyle-focused non-interactive text messaging service resulted in a modest improvement in LDL cholesterol level, and a greater improvement in other cardiovascular disease risk factors (systolic blood pressure, body mass index, physical activity, and smoking status) (Chow *et al.* 2015).

Once lifestyle changes become insufficient, optimal health outcomes in public health require both efficacious medications and adherence to those treatments. The physician's awareness of interventions aiming at improving adherence, their clinical expertise in identifying patients at risk of nonadherence to statins, and the skill to increase their adherence may have a greater effect on health than any improvement in specific medications. Nevertheless, the marketing and adoption of novel drugs should be critically observed in everyday practice to avoid unnecessary high drug costs without additional health gain.

"Keep a watch also on the faults of the patients, which often make them lie about the taking of things prescribed. For through not taking disagreeable drinks, purgative or other, they sometimes die. What they have done never results in a confession, but the blame is thrown upon the physician."

Hippocrates*, Decorum XIV (Hippocrates 1923)
*Hippocrates, born 460 Before the Common Era, learned medicine and philosophy, travelled widely as a medical doctor and teacher. Many of the roughly 70 works in the "Hippocratic Collection," are not by Hippocrates but he was undeniably the "Father of Medicine."

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Heli Halava

APPENDIX

Acronyms of the lipid studies cited in this thesis

CARE	Cholesterol and Recurrent Events
IDEAL	Incremental Decrease in End points through Aggressive Lipid lowering
JELIS	Japan EPA Lipid Intervention Study
LIPID	Long-term Intervention with Pravastatin in Ischaemic Disease
LIPS	Lescol Intervention Prevention Study
WOSCOPS	West Of Scotland Coronary Prevention Study
4S	Scandinavian Simvastatin Survival Study

Medicine reimbursement system in Finland in 2016
(http://www.kela.fi/web/en/reimbursements-for-medicine-expences)

General
The medicine reimbursement system covers all permanent residents of Finland, regardless of age, wealth or address. The reimbursement is the portion of the price of a medication purchase that is paid by the SII, Finland, as part of The National Health Insurance Scheme. This scheme reimburses some of the necessary costs of prescription-only medicines. An over-the-counter product may also be granted a reimbursement status if the product is prescribed by a physician and considered to be an indispensable medicinal product.

The Finnish medicine reimbursement system consists of the basic, the lower and higher special refund categories. The categories have been graded according to medical criteria based on the severity of the disease and the necessity of the drug treatment. The medicine must have been confirmed as reimbursable and as having a reasonable wholesale price by the Pharmaceuticals Pricing Board. The reimbursed proportions have varied over time and currently set 40% for the basic, 65% for the lower and 100% for the higher special reimbursement category. From 1 January 2016, reimbursements for prescription medicines will be available only after meeting an initial deductible of €50 per calendar year.

Basic refund category: 40% of the purchase price or reference price of a medicinal product belonging to the basic refund category is reimbursed to the patient. This basic reimbursement is paid to all individuals covered by the Finnish Health Insurance Scheme.

Special refund categories: The higher special refund category diseases are considered to be serious and chronic and drug treatment necessary for the patient to restore or replace normal bodily functions, for example drugs used to treat diabetes mellitus or malignant diseases. The purchase price or reference price of a medicinal product is reimbursed to the patient in full (100%). In this category, the patient pays a non-reimbursable sum of €4.50 per transaction for each medicinal product. **The lower special refund category** consists of the diseases that are considered to be serious and chronic. The most common diseases in this group are hypertension, asthma and coronary heart disease. 65% of the purchase price or reference price of a medicinal product belonging to this category is reimbursed to the patient. The patient must obtain a medical certificate B from his or her doctor in order to confirm the nature of the disease and the need for medication to be eligible to receive reimbursement payments under the special refund categories.

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