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CHOLESTEROL, CARDIOVASCULAR RISK AND STATIN USE IN OLDER PERSONS

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“Man sieht nur, was man weiß.”
We see only what we know.

Johann Wolfgang von Goethe

ABSTRACT

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Cholesterol, cardiovascular disease and statin use in older persons.

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Older age increases the risk of developing a chronic atherosclerotic cardiovascular disease (CVD), such as coronary heart disease. Complications of CVDs, myocardial infarction or stroke often lead to loss of functional capacity or premature death. Dyslipidemia, high serum levels of total or low-density lipoprotein cholesterol (LDL-c) and low levels of high-density lipoprotein cholesterol (HDL-c), is among the most important modifiable risk factors for CVDs; it can be treated with lifestyle modifications, and with lipid-lowering drugs, primarily statins. In older persons, however, the association of cholesterol levels with cardiovascular and all-cause mortality has been inconsistent in previous studies. Furthermore, the beneficial effects of statins in older persons without previous CVD are still somewhat unclear, and older persons are more prone to adverse effects from statins.

This thesis presents a prospective cohort study (TUVA), exploring associations of cholesterol levels with mortality and the changes in cholesterol levels of a 70-year-old population in long-term follow-up. Further, prevalence of CVDs, risk factors and preventive medication use in the TUVA cohort is compared with respective prevalences in another age-matched cohort (UTUVA) 20 years later in order to examine the changes in cardiovascular risk over time. Additionally, to evaluate statin use patterns among older persons, an observational register study was conducted covering the total Finnish population aged 70 and older during 2000-2008. Based on individual-level data retrieved from national health registries, the population was classified into low, moderate and high risk groups according to estimated CVD risk. The prevalence, incidence and persistence of statin use among the risk groups was then evaluated based upon yearly statin purchases tracked from the Prescription Register.

The prospective cohort study demonstrated that low total cholesterol, LDL-c and HDL-c were associated with higher mortality in a cohort of home-dwelling 70-year-olds. However, after adjusting for traditional cardiovascular risk factors and cancer this association disappeared. Further, low total cholesterol seemed to be protective, whereas low HDL-c strongly predicted increased risk of CVD death. Cholesterol levels of those elderly who remained available for follow-up and were still home-dwelling at the age of 85 seemed to improve with advancing age. Compared to the TUVA cohort, the later born UTUVA cohort had less CVDs and their risk factors were better controlled, which was reflected in the higher use of preventive medications such as statins and antihypertensives. The register studies confirmed that statin use has increased significantly during 2000-2008 among older persons, especially among the oldest (80+) age groups and among those at high risk for cardiovascular events. Two-thirds of new statin users persisted with their use during the four years of follow-up; the most discontinuations were made during the first year of use.

In conclusion, statins are commonly used among older age groups in Finland. Most of the older statin users had a high cardiovascular event risk, indicating that the treatment is well directed towards those who are likely to benefit from it the most. No age-limits should be put on the screening and treatment of dyslipidemia in older persons, but the benefits and adverse effects of statin treatment should be carefully weighed based on an individual assessment of the person's general health status and functional capacity. Physicians should pay more attention to medication adherence, especially when prescribing preventive medications.

Keywords: *cholesterol, cardiovascular, mortality, older persons, statins*

TIIVISTELMÄ

Eveliina Upmeier
Kolesteroli, valtimosairausriski ja statiinien käyttö iäkkäillä.

Turun yliopisto, Lääketieteellinen tiedekunta, Geriatrian oppiaine *ja*
Farmakologian, lääkekehityksen ja lääkehoidon oppiaine.
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Ikääntyminen lisää riskiä sairastua ateroskleroottisiin valtimosairauksiin, kuten sepelvaltimotautiin. Valtimosairauksien komplikaatiot, sydäninfarkti tai aivohalvaus, johtavat usein toimintakyvyn laskuun tai ennenaikaiseen kuolemaan. Dyslipidemia (suurentunut seerumin kokonais- tai LDL-kolesterolipitoisuus tai pieni HDL-kolesterolipitoisuus) on yksi tärkeimmistä valtimosairauksien riskitekijöistä, johon voidaan vaikuttaa elintapamuutoksin tai lääkehoidolla, ensisijaisesti statiineilla. Iäkkäillä henkilöillä kolesteroliarvojen yhteys valtimosairauksista johtuviin kuolemiin tai kokonaiskuolleisuuteen on ollut ristiriitainen aiemmissa tutkimuksissa. Epäselvää on, miten paljon statiinihoidosta hyötyvät ne iäkkäät, joilla ei ole aikaisempaa valtimosairautta. Ikäihmiset ovat myös herkempiä saamaan sivuvaikutuksia statiinihoidosta.

Tässä väitöskirjassa selvitetään seerumin kolesteroliarvojen yhteyttä kuolleisuuteen ja ikääntymiseen liittyviä kolesteroliarvojen muutoksia perusten Turun Vanhustutkimuksen (TUVA) 70-vuotiaista koostuvan kohortin pitkäaikaisseurantaan. Lisäksi vertailemme valtimosairauksien ja niiden riskitekijöiden esiintyvyyttä sekä ennalta ehkäisevien lääkehoitojen käyttöä TUVA kohortin ja 20 vuotta myöhemmin kerätyn uuden 70-vuotiaiden kohortin (UTUVA) väestöissä. Väitöskirjaan kuuluu myös 70 vuotiaiden ja sitä vanhempien suomalaisten statiinien käyttöä vuosina 2000–2008 koko väestön tasolla selvittävä rekisteripohjainen tutkimus. Tutkimusta varten koko Suomen iäkäs väestö luokiteltiin valtimosairauksien suhteen kolmeen riskiryhmään perustuen valtakunnallisista terveydenhuollon rekistereistä saatuihin tietoihin henkilöiden aiemmasta sairastuvuudesta ja lääkkeiden käytöstä. Statiininkäytön vallitsevuutta, ilmaantuvuutta ja käytön jatkuvuutta (persistenssiä) selvitettiin perustuen KELAn reseptirekisteristä saatuihin tietoihin kohdeväestön vuosittaista statiiniostoista.

TUVA kohortin 70-vuotiaiden kotona asuvien henkilöiden matala kokonaiskolesteroli-, LDL-ja HDL-kolesterolipitoisuus oli yhteydessä lisääntyneeseen kuolemanriskiin 12 vuoden seurannassa, mutta kun analyyseissa vakioitiin muiden kuolleisuutta lisäävien riskitekijöiden vaikutus, niin em. yhteys hävisi. Sen sijaan matala kokonaiskolesteroli näytti vähentävän ja matala HDL-kolesteroli selvästi lisäävän riskiä kuolla valtimosairaustapahtumaan. Seurannassa 85 vuoden ikään asti olleiden ja edelleen kotona asuvien iäkkäiden kolesteroliarvot paranivat iän lisääntyessä. Kohorttien vertailututkimuksessa myöhemmin tutkitun kohortin väestöllä oli vähemmän valtimosairauksia ja heidän riskitekijänsä olivat paremmin kontrollissa näkyen mm. preventiivisen lääkehoidon, kuten statiinien ja verenpainelääkkeiden lisääntyneessä käytössä. Rekisteritutkimukset osoittivat, että iäkkään väestön statiinien käyttö on lisääntynyt Suomessa huomattavasti, etenkin vanhimmissa (80+) ikäluokissa ja suuren valtimotautiriskin omaavilla henkilöillä. 2/3 uusista statiinin aloittajista jatkoi lääkitystään säännöllisesti 4 vuoden seurannan ajan; pääosa käytön keskeytyksistä tapahtui ensimmäisen käyttövuoden aikana.

Yhteenvetona todetaan, että statiineja käytetään Suomessa paljon vanhimmissa ikäryhmissä. Suurimmalla osalla iäkkäistä statiininkäyttäjistä oli suuri valtimosairaustapahtuman riski, viitaten siihen, että hoito on oikein ohjautunut niille, jotka todennäköisesti siitä eniten hyötyvät. Dyslipidemian seulonnalle ja hoidolle ei tulisi asettaa ikärajoja, mutta hoitopäätöksiä iäkkäiden kohdalla tehtäessä täytyy statiinihoidon hyödyt ja haitat arvioida jokaisen kohdalla yksilöllisesti, huomioiden henkilön kokonaisterveydentila ja toimintakyky. Lääkärien tulisi myös huomioida potilaidensa lääkehoitoon sitoutuminen aiempaa paremmin, etenkin ennalta ehkäiseviä lääkityksiä määrätessään.

Avainsanat: *kolesteroli, valtimosairaudet, kuolleisuus, iäkkäät, statiinit*

TABLE OF CONTENTS

ABBREVIATIONS

AE	adverse effects
ARR	absolute risk reduction
ATC	Anatomical Therapeutic Chemical
BMI	body mass index (kg/m^2)
BP	blood pressure
CABG	coronary artery bypass grafting
CHD	coronary heart disease
CK	creatinine kinase
CTT	Cholesterol Treatment Trialists
CVD	cardiovascular disease
DM	diabetes mellitus
FDA	Food and Drug Administration
FH	familial hypercholesterolemia
FIMEA	Finnish Medicines Agency
HDL-c	high-density lipoprotein cholesterol
HmG-CoA	hydroxymethylglutaryl-coenzyme A
ICD-9/10	international classification of diseases, $9^{th}/10^{th}$ revision
LDL-c	low-density lipoprotein cholesterol
MI	myocardial infarction
MPR	medication possession ratio
NIHW	National Institute of Health and Welfare
NNT	Number needed to treat
PAD	peripheral artery disease
PDC	proportion of days covered
PTCA	percutaneous transluminal coronary angioplasty
RCT	randomized controlled trial
RR	relative risk
RRR	relative risk reduction
SCORE	systematic coronary risk evaluation
SII	Social Insurance Institution
TC	total cholesterol
TIA	transient ischemic attack
TUVA	Turun Vanhustutkimus (Turku Elderly Study)
UTUVA	Uusi Turun Vanhustutkimus (New Turku Elderly Study)
WHO	World Health Organization

Randomized controlled trials

ASCOT-LLA	Anglo-Scandinavian Cardiac Outcomes trial-Lipid Lowering Arm
AURORA	Rosuvastatin and cardiovascular events in patients undergoing hemodialysis
CARDS	Collaborative Atorvastatin Diabetes Study
CARE	Cholesterol and Recurrent Events
CORONA	Rosuvastatin in older patients with systolic heart failure
GISSI-HF	Effect of rosuvastatin in patients with chronic heart failure
HPS	Heart Protection Study
JUPITER	Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
LIPID	Long-term Intervention with Pravastatin in Ischaemic Disease
METEOR	Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis
PROSPER	Prospective Study of Pravastatin in the Elderly at Risk
REVERSAL	Reversing Atherosclerosis with Aggressive Lipid Lowering
4S	Scandinavian Simvastatin Survival Study
SPARCL	Stroke Prevention by Aggressive Reduction in Cholesterol Levels
TNT	Treating to New Targets

LIST OF ORIGINAL PUBLICATIONS

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

I Upmeier E, Lavonius S, Lehtonen A, Viitanen M, Isoaho H, Arve S. Serum lipids and their association with mortality in the elderly: a prospective cohort study. Aging Clin Exp Res 2009; 21:424-430.

II Upmeier E, Lavonius S, Heinonen P, Viitanen M, Isoaho H, Arve S, Lehtonen A. Longitudinal changes in serum lipids in older people. The Turku Elderly Study 1999-2006. Age Ageing 2011; 40(2):280-283. (Research letter.)

III Upmeier E, Vire J, Korhonen MJ, Wuorela M, Viitanen M, Isoaho H, Lehtonen A, Arve S. Cardiovascular risk profile and use of statins at the age of 70 years: a comparison of two Finnish birth cohorts born 20 years apart. Age Ageing 2016; 45(1):84-90.

IV Upmeier E, Korhonen MJ, Helin-Salmivaara A, Huupponen R. Statin use among older Finns stratified according to cardiovascular risk. Eur J Clin Pharmacol 2013; 69(2):261-267.

V Upmeier E, Korhonen MJ, Rikala M, Helin-Salmivaara A, Huupponen R. Older statin initiators in Finland— cardiovascular risk profiles and persistence of use. Cardiovasc Drugs Ther 2014; 28(3):263-272.

1 INTRODUCTION

Through vast improvements in the prevention and treatment of cardiovascular diseases (CVD) during the past decades, the incidence of cardiovascular events has decreased in most Western countries and shifted from middle-aged persons towards the more aged population (Vartiainen *et al.* 2010, European Heart Network: European statistics 2012, Heart disease and stroke statistics, Update 2014). Parallel to the declining incidence, the fatality of CVD events has declined, leading to a higher prevalence of older survivors of myocardial infarction (MI) or stroke (Crimmins *et al*. 2011, Heart disease and stroke statistics, Update 2014). With increasing life expectancy, the population of Finland is now among the fastest aging populations in Europe, which means that we are faced with a growing number of persons with chronic diseases, such as CVD and dementia (Ministry of Social Affairs and Health Finland, 2012). The issue of whether the prevention of CVD events, by emphasizing known risk factors, is still worthwhile in individuals over 70 or 80 years old is therefore important in the field of geriatric medicine today.

Hypercholesterolemia, elevated total cholesterol (TC) and, a high level of low-density lipoprotein cholesterol (LDL-c) in the plasma in particular, is a major risk factor for atherosclerotic CVD, most importantly for coronary heart disease (CHD) (Kannel *et al.* 1964, Lewington *et al*. 2007, Ridker *et al*. 2014). In contrast, high-density lipoprotein cholesterol (HDL-c) has atheroprotective properties and its plasma level is inversely associated with the CVD risk (Kannel *et al.* 1964, Rader and Hovingh 2014). Epidemiologic evidence consistently shows that high TC and LCL-c are directly associated with higher CVD morbidity and mortality in adults (Stamler *et al*. 1999, Lewington *et al*. 2007). In older persons ("*older*" referring to persons 70 years and older in this thesis), however, the association between elevated TC/LDL-c levels and CVD risk diminishes (Kronmal *et al.* 1993, Kannel *et al.* 2002, Lewington *et al.* 2007). Results from epidemiologic studies of older populations have been conflicting, some showing a lack of association (Krumholz *et al*. 1994, Psaty *et al*. 2004, Jacobs *et al.* 2013), or U-shaped association (Castelli *et al.* 1989, Curb *et al.* 2004); most studies, however, have observed an inverse association between TC/LDL-c levels and mortality (Weverling-Rijnsburger *et al.* 1997, Schatz *et al.* 2001, Brescianini *et al*. 2003, Schupf *et al.* 2005, Takata *et al.* 2014). This so-called cholesterol paradox has raised questions concerning the treatment of hypercholesterolemia in older age (Desai *et al*. 2011, Morley 2011).

Since the 1990s, strong evidence from several large-scale randomized controlled trials (RCTs) have established the major role of HMG-CoA inhibitors, that is, statins, in lowering the LDL-c levels, thereby preventing cardiovascular events and decreasing mortality in different populations with risk factors for CVD (Scandinavian Simvastatin Survival (*4S*) Study group 1994, Shepherd *et al.* 1995, Sacks *et al*. 1996, Long-term Intervention with Pravastatin in Ischemich Disease (*LIPID*) study group 1998, Heart

Protection Study (*HPS*) Collaborative Group 2002). Older persons, especially older women, have been underrepresented in these trial populations, even though subgroup analyses (Lewis *et al.* 1998, Hunt *et al*. 2001, HPS Collaborative Group 2005) and meta-analyses (Baigent *et al.* 2005, Afilalo *et al*. 2008, Mihaylova *et al.* 2012) have later reported similar beneficial effects from statin treatment among older individuals. The "Prospective study of pravastatin in elderly individuals at risk of vascular disease" (PROSPER) is, to date, the only RCT on the effects of statins specifically designed for older persons. It failed to show reduction in all-cause mortality with statin treatment, but significant reductions in CVD mortality and event rates were seen among the high-risk population of the study (Shepherd *et al.* 2002). During the last decade, several observational studies based on hospital discharge registers have reported that among old high-risk persons statin users live longer than non-users (Allen Maycock *et al.* 2002, Cooke *et al.* 2009, Gränsbo *et al.* 2010).

According to recent guidelines (Finnish Dyslipidemia Current Care Guidelines 2013, Catapano *et al.* 2011, Stone *et al*. 2014), statins should be prescribed to all individuals with existing CVD, regardless of age or LDL-c level. In individuals free of CVD, treatment decision should be based on the estimation of the persons' total cardiovascular risk. In older age, however, the definition of "risk" becomes more complex. Older age, in general, means a higher risk and most fatal CVD events occur to persons aged over 70 years (Heart disease and stroke statistics Update 2014, Statistics Finland 2014). Statin treatment is widespread across all ages in Finland (Ruokoniemi *et al*. 2008); however, recent trends in statin use among older age groups need clarification, as both underuse (Robinson *et al*. 2010, Candrilli *et al.* 2010) and overuse (referring to channeling of use towards low-risk persons) (Wallach Kildemoes *et al.* 2012) have been observed in previous studies. Moreover, studies on medication adherence have reported poor continuity rates among statin users, which is an important issue and potentially leads to growing rates of CVD events (Chowdhury *et al*. 2013).

This thesis reviews and further complements the research dealing with cholesterol as a risk factor for CVD and mortality, and the use of statins in CVD prevention in older persons. The associations between cholesterol levels and mortality are derived from a longitudinal follow-up of a 70-year-old population cohort in the "Turku Elderly Study" (TUVA). Further, the original cohort, and a new 70-year-old cohort recruited 20 years later from the same Turku area, are characterized and compared in terms of their CVD morbidity, risk factor profiles and medication use (with the focus on statins). The second part of the study, a nationwide register study among older Finns, investigates the population level trends in statin use, channeling of statin use according to individual CVD risk status, and persistence (continuity) of statin use.

2 REVIEW OF THE LITERATURE

2.1 Cardiovascular disease and aging

CVDs are a group of disorders affecting heart and blood vessels (arteries). The most important clinical CVDs causing the most deaths are coronary heart disease (CHD) and cerebrovascular disease, including stroke and transient ischemic attack (TIA). In addition, peripheral artery disease (PAD) and aortic aneurysms are manifestations of atherosclerotic CVD (World Health Organization (WHO) 2011a). On the other hand, hypertension, albeit a disease of blood vessels, is typically considered a risk factor for and not an existing CVD in guidelines and treatment studies (Perk *et al*. 2012). In Finland, about 40% of all mortality is due to CVD, even though there has been a decreasing trend in the incidence of fatal and nonfatal CVD events during the past decades (National Institute of Health and Welfare (NIHW) statistical database 2015, Vartiainen *et al*. 2010, Kattainen *et al.* 2006).

The traditional risk factors of atherosclerotic CVD are high age, male sex and, as modifiable risk factors, hypertension, hyperglycemia, smoking and dyslipidemias, including high LDL-c, low HDL-c and, to a lesser extend, high triglycerides (Perk *et al*. 2012). Type 2 diabetes mellitus (DM) is often characterized by highly atherogenic dyslipidemia and, at its worst, it doubles the individual's CVD event risk (Matikainen *et al*. 2010). Thus, DM has been considered a CVD-equivalent in treatment guidelines (Catapano *et al*. 2011). Untreated hypertension may eventually lead to target organ damage and it increases the risk of renal failure, cerebrovascular disease, CHD, heart failure or atrial fibrillation (Perk *et al*. 2012). Typically, the same individuals have several co-existing risk factors leading to higher cumulative CVD event risk; therefore, the use of risk estimation charts is recommended (Catapano *et al*. 2011, Perk *et al*. 2012). Beyond the traditional risk factors, many novel risk factors have been detected associating with CVD risk, for example serum apolipoproteins, high sensitivity C-reactive protein or coronary artery calcification scores (Sniderman *et al.* 2011, Perk *et al.* 2012).

Aging is a major non-modifiable risk factor for CVD, and worldwide most cardiovascular events occur to persons aged over 65 (Heart disease and stroke statistics update 2014). In Finland, 9 out of 10 persons dying of CVD are over 65 years old and nearly half of them over 75 years old (Statistics Finland 2014). Older persons are more susceptible to CVD events since they often have subclinical atherosclerosis due to multiple lifetime accumulated risk factors, such as hypercholesterolemia, high blood pressure (BP) or smoking. With older age, the systolic BP tends to rise, impaired glucose tolerance and type 2 DM become more common and sedentary lifestyle of older persons adds to the risk (Kannel *et al.* 2002, Felix-Redondo *et al*. 2013). It is estimated that over 20% of persons aged 70 and older have type 2 DM, and the prevalence is expected to be

increasing worldwide due to increasing obesity and prevalence of metabolic syndrome among older adults (DECODE Study Group 2003, Grundy *et al*. 2005). Moreover, dyslipidemia, hypertension and type 2 DM all increase the risk of developing chronic kidney disease (CKD), which in itself is a condition associated with high cardiovascular event risk (Perk *et al*. 2012).

2.2 From cholesterol to cardiovascular disease

2.2.1 Cholesterol, lipoproteins and apolipoproteins

Cholesterol has an essential role in the function of cell membrane structures and in hormone and vitamin synthesis. The cholesterol circulating in our blood originates from three sources: the intestinal absorption of food, bile salts secreted by the liver, and cellular synthesis, mainly in the liver. Normally, a homeostasis is maintained between intestinal absorption and synthesis of cholesterol adapting to the individual's needs (Genest J. 2003, Goldstein and Brown 2009). Dietary fats (triglycerides, cholesterol, cholesteryl esters and phospholipids) absorbed from the intestinal lumen are packed in chylomicrons to be transported in the blood. With the help of the lipoprotein lipase (LPL) enzyme, the triglycerides in chylomicrons release free fatty acids (FFA) for the use of the muscle cells and for storage in adipose tissue. The remaining cholesterol and triglycerides in chylomicrons are then transported to the liver for further use. Endogenic lipids synthesised in the liver are transported in three major lipoprotein particles: very-low density lipoproteins (VLDL or "remnant cholesterol"), LDL and HDL. The chylomicron-lipoprotein transport system has several important functions, including the transport of dietary fats from the intestine to the liver, the transport of processed cholesterol particles to the peripheral tissue, the processing of free fatty acids and, finally, the reverse cholesterol transport (Genest 2003, Välimäki *et al*. 2009) (Figure 2.1).

All lipoproteins contain apolipoproteins, which regulate their transport and metabolic pathways. The atherogenic apolipoprotein (apo) B is found in VLDL and in LDL. The apoB containing VLDL particles transport triglycerides and cholesterol for the needs of the body. The LDL particles (derived from VLDL) are the main carrier of cholesterol (about 60%) to peripheral tissues and are therefore presumably responsible for the initiation of atherosclerosis (Genest J. 2003, Välimäki *et al*. 2009)**.** Cellular uptake of cholesterol is regulated by LDL receptors. Part of the circulating LDL is returned to the liver. The LDL receptors in the liver regulate the level of LDL-c in the blood (Goldstein and Brown 2009) (Figure 2.1). Genetic disorders of the LDL receptor, such as familial hypercholesterolemia (FH), lead to excessive LDL-c concentration, which in turn leads to early atherosclerosis (Sniderman *et al.* 2014).

The most important apolipoprotein in HDL is (apo) A-1. The HDL precursor (preβ-HDL) is synthesised both in the intestine and the liver. Mature HDL particles (subfractions HDL_3 and HDL_2) undergo a complicated process regulated by several enzymes, including

lecithin cholesterol acyltransferase (LCAT) and cholesteryl ester transfer protein (CETP). HDL transports about 30% of the plasma cholesterol and is responsible for the reverse cholesterol transport, an atheroprotective process in which excess cellular cholesterol is returned to the liver to be reused in the lipoprotein synthesis or excreted in the bile (Schaefer *et al.* 2014) (Figure 2.1).

Triglyceride-rich lipoproteins serve as an energy storage, and their plasma level is inversely associated with the HDL-c level (Nordestgaard and Varbo. 2014). While the TC, HDL-c and triglyceride concentrations are determined directly from the plasma, LDL-c concentration is typically calculated by the Friedewald equation (Friedewald *et al*. 1972), based on the concentrations of TC, HDL-c and triglycerides. In some disease conditions, such as type 2 DM or metabolic syndrome, the number of particularly atherogenic small dense LDL particles may be increased, even though the total LDL-c concentration is within the normal range. In such cases, the determination of plasma apolipoprotein concentrations (apoA-1 and apoB) might be useful in total cardiovascular risk assessment (Sniderman *et al*. 2011).

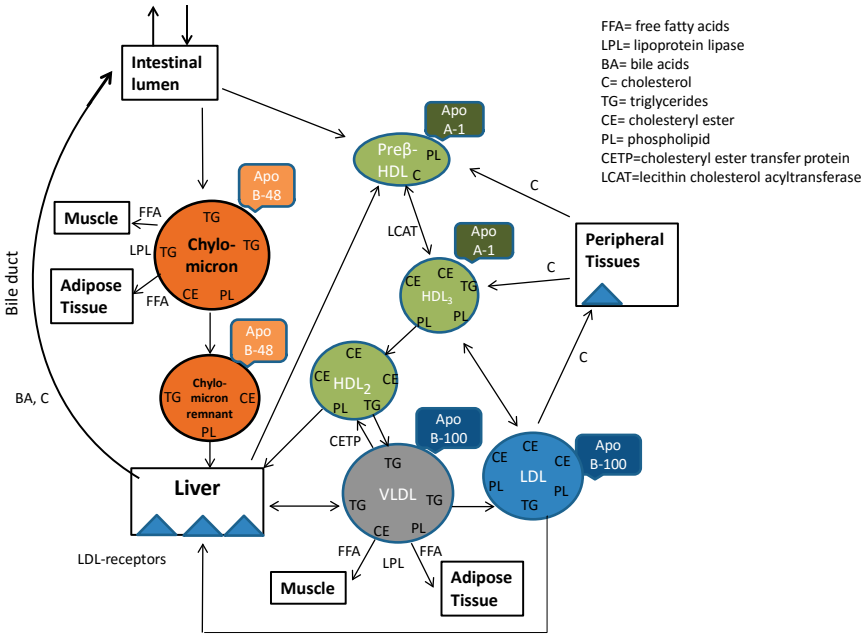

Figure 2.1 Cholesterol transport and metabolism. Dietary fats are absorbed from the intestine, packed in chylomicrons and transported in the blood via the lipoprotein transport system. Several enzymes participate in the metabolic processes. The liver is the main organ for cholesterol synthesis and regulation of blood cholesterol levels through LDL receptors. HDL has an important function in transporting excess cellular cholesterol from peripheral tissues back to the liver (to be re-processed or excreted in the bile).

2.2.2 Atherosclerosis

Atherosclerosis is a chronic, progressive disease with a long asymptomatic phase. The pathophysiology of the disease is not yet completely understood, but it is believed to result from a chronic inflammation and injury to an arterial vessel wall (Genest 2003, Lardizapal and Deedwania 2011). A high plasma LDL-c level, along with several other factors, enhances the progression of atherosclerosis. LDL-c and its oxidation initiate a series of events leading to the process where fatty streaks are accumulated and later progressed to atherosclerotic plaque-formation in the intimal layer of the arteries (Navab *et al.* 2004). In contrast, HDL-c has functions, such as the reverse cholesterol transport, that may inhibit this process, and it has been presented that the balance between the two lipoproteins determines the rate and severity of the progression of atherosclerotic diseases (Navab *et al.* 2004). The development of atherosclerosis, atherogenesis, begins at an early age and takes years to progress from a subclinical state to a symptomatic clinical disease. During the process, the plaques in arterial walls begin to grow toward the vessel lumen, producing stenosis and/or thrombosis and eventually leading to ischemia and different manifestations of CVD. Typical complications of atherosclerotic CVD are MI, ischemic stroke or sudden cardiac death (Perk *et al*. 2012).

2.2.3 Evidence for the associations

FH is a classic example of the association of high LDL-c and increased CVD risk (Sniderman *et al.* 2014). Individuals with FH have intrinsically high LDL-c levels, leading to an increased risk of CVD events already at a young age: those with homozygous FH suffer ischemic events (MI) in their 20s or even earlier, and those with heterozygous FH at the age of 30-40, whereas in healthy individuals the onset of CVD manifestations is typically at the age of 50 or 60 (Sniderman *et al.* 2014).

The causal association of TC or LDL-c with atherosclerotic CVD is established in several prospective epidemiologic studies, trials with cholesterol-lowering drugs and more recently by genetic studies with Mendelian randomization models (Ference *et al*. 2012, Ridker *et al.* 2014,). The first real prospective cohort study, the Framingham Heart Study, was initiated in 1948 to examine and establish risk factors for CVD (Mahmood *et al*. 2014), and it produced evidence supporting the association of cholesterol levels and CHD as early as in the 1960s (Kannel *et al.* 1964). The Seven Countries Study (Keys 1997) and other epidemiologic studies from different countries have since confirmed the results derived from the Framingham cohort (Lewington *et al*. 2007). Further, in multiple placebo-controlled trials since the late 1980s, cholesterol-lowering drugs, mainly statins, have successfully lowered elevated TC and LDL-c levels, correlating with a decrease in CVD events and mortality (Baigent *et al*. 2005, Mihaylova *et al*. 2012).

The plasma level of HDL-c has been inversely associated with CVD and mortality in several prospective studies (Kannel *et al*. 1964, Toth *et al*. 2013). Low levels of HDL-c

have predicted higher mortality and, especially in populations consisting of older persons, this association has been strong (Corti *et al.* 1995, Weverling-Rijnsburger *et al.* 2003). However, the atheroprotective role of HDL-c has recently been compromised due to the lack of clinical benefits in trials with HDL-increasing drug therapies (Rader and Hovingh 2014). In addition, genetic studies have failed to show an association between low HDL-c plasma levels and CVD events. Consequently, it has been suggested that it is not the HDL itself but its function (in reverse cholesterol transport) that may have a causal relation to atheroprotection (Rader and Hovingh 2014).

The role of triglycerides in the development of atherosclerosis is not yet established even though there is increasing evidence from both epidemiologic and genetic studies that hypertriglyceridemia contributes to the exacerbation of atherosclerotic conditions (Nordestgaard and Varbo 2014). Fibrates are beneficial in patients with severe hypertriglyceridemia (Wierzbicki and Viljoen 2014). However, large trials with drugs that lower the concentrations of triglycerides are lacking and, it is unclear, whether triglyceride-lowering drugs have additive benefits in terms of CVD morbidity or mortality when combined with statin therapy (Nordestgaard and Varbo 2014).

2.3 Cholesterol and the aging process

There are several changes in plasma cholesterol levels during aging. TC and LDL-c seem to increase gradually after puberty until about the age of 60-65 in men, after which they slowly begin to decrease; in women, this change occurs 5-10 years later due to the influence of estrogen (Carroll *et al*. 2005, Felix-Redondo *et al*. 2013). In cross-sectional studies, men aged > 65 years have had lower TC levels than younger men, mainly due to diminished LDL-c levels (Abbot *et al.* 1983, Carroll *et al.* 2005). In the Helsinki Businessman study, a cohort of middle-aged men were followed for 39 years and the cholesterol levels measured at baseline did not necessarily correlate with the levels measured in old age; in some cases, high cholesterol levels measured at middle-age had decreased to normal by the time the individuals reached old age (Strandberg *et al*. 2004). HDL-c changes less during adulthood, but in cross-sectional reports HDL-c tends to be higher in older age groups (Ettinger *et al*. 1992, Carroll *et al*. 2005). Results from longitudinal studies assessing changes in cholesterol levels, however, have been inconsistent (Wilson *et al*. 1994, Weijenberg *et al*. 1996, Ferrara *et al*. 1997, Abbot *et al.* 1998), and due to the widespread use of cholesterol-lowering drugs it has become even more challenging to observe the physiological age-related changes in cholesterol levels.

Cholesterol metabolism undergoes changes with increasing age. A Finnish study group measured serum TC, lathosterol (a cholesterol precursor that reflects cholesterol synthesis) and sitosterol (which reflects cholesterol absorption) in a cohort of > 75-year-old persons and concluded that old age is characterized by both decreasing cholesterol synthesis and decreasing cholesterol absorption, which in turn lead to

lowered TC levels (Tilvis *et al.* 2011). In that study, low levels of all three sterols independently correlated with poorer health status and predicted diminished survival in a 17-year follow-up.

Low cholesterol levels in old age (low TC, LDL-c, and HDL-c) have been associated with low albumin levels and frailty in population studies (Zuliani *et al.* 1999, Hazzard *et al.* 2001, Schalk *et al*. 2004,). Frailty is a condition observed in elderly people, especially in older women, and it is characterized by fatigue, slow gait speed, and unintentional weight and muscle loss (Singh *et al.* 2014). It is known to increase the risk of institutionalization and death. Furthermore, low TC levels in 90-year-olds have been associated with high interleukin-6 levels in a cross-sectional study (Lehtimäki *et al*. 2005), indicating that low cholesterol levels reflect inflammation processes. Chronic inflammation or subclinical diseases (e.g. dementia or cancer) may lower the cholesterol levels years before the actual manifestation of the disease (Schatz *et al.* 2001, Schupf *et al*. 2005). Thus, low cholesterol levels in old age can be considered a marker of deteriorating health and, as such, indicative of a reduced life expectancy (Tilvis *et al*. 2011).

2.4 Cholesterol as a risk predictor in older age

In adult populations, the direct associations of elevated TC and LDL-c with cardiovascular and total mortality have been established by several longitudinal studies (Kannel *et al* 1964, Stamler *et al.* 1999, Lewington *et al.* 2007). In elderly people, however, this association seems to be reversed: low TC levels, when measured in old age have been shown to correlate with worse prognosis and increased mortality of all causes (Schatz *et al*. 2001, Schupf *et al*. 2005, Takata *et al.* 2014). In the Honolulu Heart Program follow-up, older men with the lowest TC levels at the beginning of the study were the ones most likely to die by the end of the 20-year follow up (Schatz *et al*. 2001). Further, a U-shaped association has been found in some studies (Jacobs *et al*. 1992, Curb *et al*. 2004), apparently caused by the fact that high TC increases the risk of atherosclerotic disease events and low TC has been associated with increased mortality for non-atherosclerotic conditions. In contrast to studies reporting on reverse associations, a large scale observational study (Corti *et al.* 1997) reported that after adjustment for established risk factors for CVD and markers for poor health (such as low iron and albumin levels), higher cholesterol levels predicted mortality in the same way in older as in younger individuals. Similar observations on the direct association of high TC or LDL-c to CVD events and/or mortality have been reported by some other studies with older populations (Aronow and Ahn 1996, Lloyd-Jones *et al.* 2003). (Tables 2.1, 2.2)

Later, a large meta-analysis of 61 prospective studies in individuals without previous CVD reported that high TC levels predicted increased CHD mortality also in persons aged 70-89, although less strongly than in younger age groups (Lewington *et al.* 2007,

Figure 2.2). Interestingly, the direct association of TC with stroke mortality disappeared in the subgroup composed of persons aged 70 or older.

In older age, LDL-c seems to be less important as a risk predictor than HDL-c (Castelli *et al*. 1989, Corti *et al*. 1995, Packard *et al*. 2005). In a Dutch cohort of persons aged 85 and older, low HDL-c, but not LDL-c, strongly predicted CHD and stroke mortality in a 4-year follow-up (Weverling-Rijnsburger *et al*. 2003). A follow-up study of a primary prevention cohort of 65-year-olds (Cardiovascular Health Study) revealed no association between cholesterol levels and the combined end-point, including CVD events and total mortality (Psaty *et al.* 2004). However, a strong independent association of low HDL-c and MI risk was observed in the same cohort (Tables 2.1, 2.2.). In a statin trial with older subjects, the baseline LDL-c level was not related to the risk of CVD events, nor was the LDL-c level achieved with therapy linked to risk reduction (Packard *et al*. 2005). Furthermore, individuals with the lowest HDL-c levels had a two-fold increase in coronary events compared to those with the highest HDL-c. In population studies, high HDL-c has been associated with longevity and a better general health status (Schaefer *et al*. 1989, Postiglione *et al.* 1989.

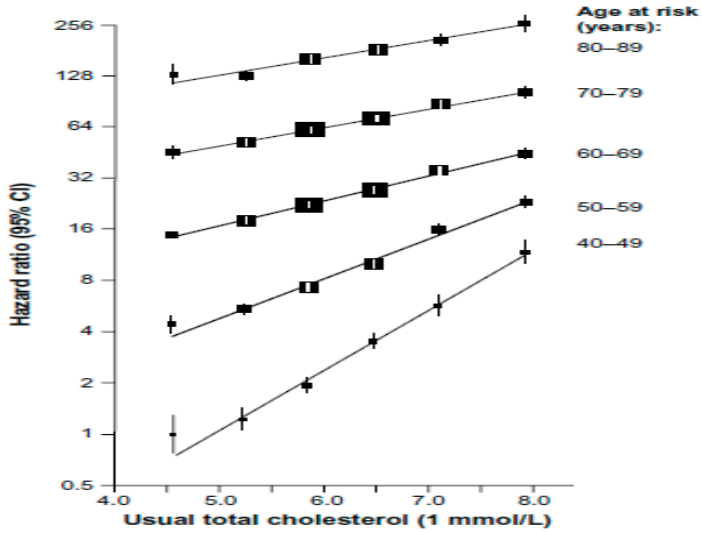

Figure 2.2 Vascular mortality according to age and total cholesterol level in the Prospective Studies Collaboration (Figure from Lewington *et al.* 2007, reproduced with permission from Elsevier.)

Table 2.1 Epidemiologic studies on the association of cholesterol levels with cardiovascular (CVD) mortality in older persons

Study	**Cohort (n)**	**Male %**	**Age**	**Follow-up (years)**	**Association of TC/LDL-c with CVD mortality**	**Association of HDL-c with CVD mortality**
Benfante *et al*. 1990	HHP (1480)	100	≥ 65	12	direct (CVD events)	not reported
Rubin *et al*. 1990	Kaiser (2746)	100	60-79	10	direct	not reported
Wong *et al*. 1991	FHS (374)	70	33-88 (mean 62)	10.5	direct	not reported
Zimetbaum *et al*. 1992	Bronx (350)	35	75-85	10	not reported	inverse (in men)
Kronmal *et al*. 1993	FHS (5209)	not reported	analyses at ages* 40,50,60,70, 80	biennial examinations from 1948 to 1980	direct at 40, 50, 60 (none later)	not reported
Krumholz *et al*. 1994	EPESE (997)	not reported	over 70	4	no association	no association
Corti *et al*. 1995	EPESE (3904)	35	over 70	4.4	no or weak association	inverse
Aronow and Ahn 1996	prospective cohort (2152)	31	60-100	3	direct	inverse
Corti *et al.* 1997	EPESE (4066)	not reported	over 70		direct	not reported
Psaty *et al.* 2004	CHS (5201)	38	≥ 65	7.5	no or weak association	inverse (CVD events)
Weverling-Rijnsburger *et al*. 2003	Leiden (599)	34	≥85	4	no association	inverse

*Age-specific analyses of survival at ages 40, 50, 60, 70 and 80 years

TC = total cholesterol; LDL-c = low-density lipoprotein cholesterol; HDL-c = high-density lipoprotein cholesterol; CVD = cardiovascular disease

HHP = Honolulu Heart Program; Kaiser = Kaiser Permanente Coronary Heart Disease in the Elderly Study; FHS = Framingham Heart Study; Bronx = Bronx Aging Study; EPESE = Established Populations for Epidemiologic Studies in the Elderly; CHS = Cardiovascular Health Study; Leiden = Leiden 85-plus study

Table 2.2 Epidemiologic studies on the association of cholesterol levels with all-cause mortality in older persons

Study	**Cohort (n)**	**Male %**	**Age**	**Follow-up (years)**	**Association of TC/LDL-c with mortality**	**Association of HDL-c with mortality**
Wong *et al*. 1991	FHS (374)	70	33-88 (mean 62)	10.5	direct	not reported
Zimetbaum *et al*. 1992	Bronx (350)	35	75-85	10	not reported	inverse (in men)
Kronmal *et al.* 1993	FHS (5209)	not reported	analyses at ages* 40/50-70 /80	biennial examinations from 1948 to 1980	direct/none /inverse	not reported
Krumholz *et al*. 1994	EPESE (997)	not reported	>70	4	no association	no association
Weverling-Rijnsburger *et al*. 1997	Leiden (724)	28	≥85	10	inverse	not reported
Schatz *et al.* 2001	HHP (3572)	100	71-93	20	inverse	not reported
Psaty *et al*. 2004	CHS (5201)	38	≥65	7.5	no (weak) association	no association
Schupf *et al.* 2005	Manhattan (2277)	34	65-98	3	inverse	no association
Tuikkala *et al.* 2010	Kuopio (490)	28	≥75	6	inverse	not reported
Jacobs *et al.* 2013	Jerusalem (460)	53	≥70	15	no association	not reported
Takata *et al.* 2014	Japan (207)	44	85	10	inverse	not reported

*Age-specific analyses of survival at ages 40, 50, 60, 70 and 80 years

TC = total cholesterol; LDL-c = low-density lipoprotein cholesterol; HDL-c = high-density lipoprotein cholesterol

HHP = Honolulu Heart Program; FHS = Framingham Heart Study; Bronx = Bronx Aging Study; EPESE = Established Populations for Epidemiologic Studies in the Elderly; Leiden = Leiden 85-plus study; CHS = Cardiovascular Health Study; Manhattan = Prospective study in Medicare recipients aged 65 and older residing in Northern Manhattan; Kuopio = Kuopio 75+ Health Study; Jerusalem = Jerusalem Longitudinal Cohort Study;
Japan = Prospective cohort study in 85-year-old Japanese population

2.5 Treatment of dyslipidemia in cardiovascular disease prevention

In populations where CVDs are uncommon, the average plasma TC levels are under 3.2 mmol/l (Cambell *et al*. 1998). However, the risk of CVD already begins to increase when LDL-c exceeds 1 mmol/l (Grundy *et al.* 2004). Physiologically low LDL-c levels, as measured in contemporary hunter-gatherer populations are below 1.5 mmol/l, even as low as 0.65 mmol/l, but in a typical Western population LDL-c is generally between 2.3-3.3 mmol/l and TC around 5.2 mmol/l (LaRosa *et al.* 2013). In the general population, the most common reasons for elevated LDL-c levels and hence an increased risk for CVD are the western diet with an excess of animal origin saturated fats and a sedentary lifestyle (LaRosa *et al.* 2013). The excess sodium intake as part of the Western diet leads to an elevated BP, consequently enhancing the risk of CVD. Cigarette smoking and impaired glucose tolerance add to the cumulative risk. Thus, the first-line treatments of dyslipidemia in the general population are lifestyle changes: a more Mediterranean-style diet (more fish oils, vegetables, fruit, and less animal fats), increased physical activity and avoidance of smoking and overweight (Finnish Dyslipidemia Current Care guidelines 2013, Perk e*t al*. 2012).

In Finland, lifestyle changes aiming at reducing CVD events have been successfully implemented in the population by the North-Karelia project which began in 1972 (Puska *et al.* 1976). The TC levels of the population have continuously declined for 35 years, but, based on the nationwide FINRISK health surveys, in the last 5-year interval (2007-2012) a slightly increasing trend in TC levels was observed (Borodulin *et al*. 2015). The mean TC levels in the surveys consisting of population samples aged 35−74 were 5.3 mmol/l in 2007, and 5.4 mmol/l in 2012 (Vartiainen *et al*. 2013). The increasing trend in cholesterol levels may reflect dietary changes in the population, such as the fashionable, protein-rich, “low-carb “-diet favoring animal fats (The FINDIET survey, Helldan *et al*. 2013).

Drug treatment of dyslipidemia is always indicated for secondary prevention of CVD events, and for primary prevention based on total cardiovascular risk estimation if the lifestyle modification is not sufficient. Statins are the first choice for medication. In addition, if statins are not tolerated or their effect remains insufficient, treatment with cholesterol absorption inhibitor (ezetimibe) is recommended, and for isolated hypertriglyceridemia fibrates and fish-oils may also be considered (Finnish Dyslipidemia Current Care guidelines 2013, Catapano *et al.* 2011).

PCSK9 inhibitors are a new class of medication for the treatment of hypercholesterolemia. Their function is based on liver *proprotein convertase subtilisin/kexin 9* (PCSK9), which participates in regulating the level of circulating LDL-c. The binding of PCSK9 to the LDL receptor leads to its cellular uptake and subsequent degradation. As a result, the number of LDL receptors in the surface diminishes and the plasma LDL-c level increases. PCSK9 inhibitors, or antibodies, inhibit the binding of PCSK9 to the LDL receptor, leaving more receptors available for LDL-uptake (Ridker

2014). Two drugs, evolokumab and alirokumab are newly available on the Finnish market. Both have managed to lower LDL-c levels by 50-70% on average when added to a statin treatment. Preliminary trial results suggest that these drugs reduce CVD events in high-risk persons in a relatively short follow-up time (Zhang *et al*. 2015); however, large outcome trials are still underway. At present, these expensive drugs are primarily indicated for the treatment of familial hypercholesterolemia and other severe forms of dyslipidemia, especially in statin intolerant individuals.

2.6 Statin treatment

2.6.1 Function and effects

Statins are potent drugs for lowering TC and LDL-c levels, and, to date, they are the only group of cholesterol modifying agents that have been proven effective in reducing CVD events in multiple RCTs (Aronow 2015, Stone *et al*. 2013). At present, there are seven different statins in use around the world: lovastatin, simvastatin, fluvastatin, pravastatin, atorvastatin, rosuvastatin and pitavastatin. All but pitavastatin are available for prescription in Finland. Statins inhibit the HMG-CoA-reductase enzyme and thereby reduce the normal cholesterol synthesis, resulting in lower serum levels of TC and LDL-c, up to 50% with the most potent statins (Figure 2.3). The influence of statins on HDL-c (up to 10% rise) or triglyserides (up to 20% reduction) is modest (Lardizapal and Deedwania 2011).

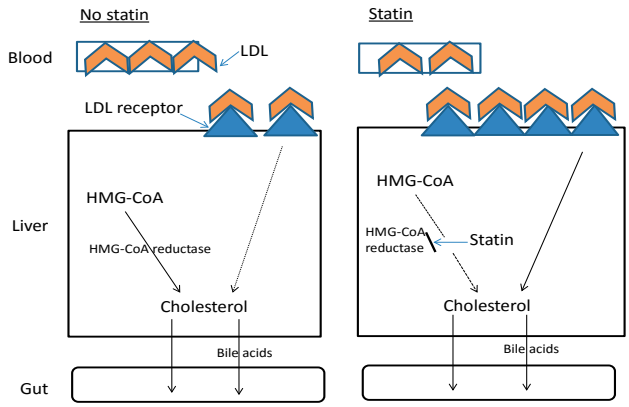

Figure 2.3 The function of statins. In liver cholesterol synthesis, cholesterol is produced from hydroxymethylglutaryl-CoenzymeA (HMG-CoA). This process is regulated by the HMG-CoA reductase. The statins act as competitive inhibitors of the HMG-CoA reductase, thereby attenuating cholesterol synthesis. Liver cells compensate for this by increasing the number of LDL receptors, which leads to a higher cellular uptake of LDL and diminished levels of circulating LDL-c in the blood.

The reduction in LDL-c and the improvement of the overall lipid profile achieved by statins has been shown to reduce CVD events in long-term use; the benefits are mostly derived from trials lasting 3-5 years. In addition, statins have slowed the progression of atherosclerotic plaque formation and facilitated the regression of atherosclerotic lesions in a relatively short time (Lardizapal and Deedwania 2011). In a trial of 500 patients with CHD (REVERSAL), 18 months of treatment with high-dose atorvastatin resulted in significant reduction in the progression of coronary atherosclerosis, as measured by intravascular ultrasonography (Nissen *et al*. 2005). In another study (METEOR), treatment with rosuvastatin significantly reduced the rate of progression of the carotid intima media thickness during 12 months of therapy in 1000 asymptomatic individuals with subclinical atherosclerosis (Crouse *et al.* 2007). Furthermore, statins have the ability to stabilize the vulnerable plaques in arterial vessel walls, which are those most likely to rupture and cause acute ischemic events (Goldenberg and Glueck 2009). The stabilization of the plaques, also known as the pleiotropic effects of statins, includes reducing LDL oxidation, inflammation and apoptosis in atherosclerotic plaques. These effects may occur after only a few months of statin treatment and are suggested to be among the most important statin mechanisms in the secondary prevention of CVD events (Marzilli *et al*. 2010, Lardizapal and Deedwania 2011).

2.6.2 Evidence on efficacy and effectiveness

The most important evidence on the efficacy of drug treatments comes from RCTs. The treatment effect in statin trials is typically presented in terms of relative risk reduction (RRR). The RRR is calculated as follows: the event rate of the placebo (or control) group minus the event rate of the treatment group divided by the event rate of the placebo group (x 100%). However, the RRR may be misleading and make the treatment effect seem larger than it is; therefore, treatment benefit should also be expressed as a reduction in the absolute risk. Even when the RRR of a specific treatment is high, the corresponding reduction in absolute event risk might be low if the incidence rate of the disease outcome (in that particular population) is low (Dorresteijn *et al.* 2011). The absolute risk reduction (ARR) is calculated simply by subtracting the event rate of the treatment group from that of the placebo group. The number needed to treat (NNT), mathematically calculated as an inverse of the absolute risk reduction, is another way of reporting the treatment benefit (Nuovo *et al*. 2002). In statin trials, the NNT defines the number of patients a clinician needs to treat with the statin for a specific period of time to prevent one cardiovascular event (or other pre-defined clinical outcome). A lower baseline risk translates into higher NNTs for treatment benefit in a given population. Furthermore, in an RCT the patient-population is analyzed as a group, but in reality the absolute treatment benefit depends on the characteristics of the individual patients (Rothwell 2005).

Table 2.3 presents the most important statin trials that have included older persons.The first large *secondary prevention* trials 4S (The Scandinavian Simvastatin Survival Study investigators 1994), CARE (Sacks *et al*. 1996) and LIPID (The Lipid Study

Group 1998) consistently demonstrated the benefits of statin treatment in reducing cardiovascular events in mainly middle-aged CHD patients, but subgroup analyses were later performed among age groups of 65 to 70-75 (Miettinen *et al*. 1997, Lewis *et al.* 1998, Hunt *et al.* 2001). Reductions in relative risks were very similar to those seen in younger people and reductions in absolute risks were even bigger in older subgroups due to the higher event rates among the older people compared to younger ones.

In the HPS trial (HPS Collaborative Group 2002), simvastatin 40mg was compared to a placebo among 20,536 high-risk individuals, of whom 5806 were aged 70-80 years at the beginning of the trial. Among the elderly subgroup, during a mean follow-up of 5 years, simvastatin reduced major CVD events by 18%, and, similarly to the entire cohort, stroke by one-quarter and all-cause mortality by 13%. The absolute event rate of major CVD events was reduced by 5.1% with simvastatin in the older subgroup compared to 5.4% in the total trial population (NNT 20 vs. 19). The beneficial effect of simvastatin on all-cause mortality was due to great reductions in deaths from (cardio)vascular causes (RRR 17%) as simvastatin had no effect on the rates of non-vascular deaths (HPS Collaborative Group 2005).

The PROSPER study (Shepherd *et al.* 2002), is to date the only statin RCT specifically designed for older persons, with 5804 participants aged 70-82 at the beginning of the study. Almost half of the participants had previous CVD and the rest had multiple risk factors. During a mean follow-up of 3.2 years, pravastatin reduced the risk of combined major CVD events (including fatal events) by 15% and major coronary events by 19% but did not reduce all-cause mortality or stroke. The 15% reduction in the relative risk of major CVD events is derived from the 2.1% units reduction in the absolute risk (which equals an NNT of 48). In the secondary prevention subgroup (44% of the baseline population who had previous CVD) absolute risk reduction was higher, 4.3% units, yielding an NNT of 23. Similar beneficial effects were not demonstrated in the primary prevention subgroup. Furthermore, the trial demonstrated the importance of HDL-c as a risk predictor in the elderly: subjects with low HDL (< 1.15) benefitted most from the pravastatin treatment (RRR for coronary events 33 vs. 19% in the whole cohort)(Packard *et al*. 2005). A post-trial follow-up of the PROSPER study cohort over 8.6 years demonstrated that the beneficial effects on coronary events achieved through pravastatin treatment during the trial were maintained long-term. However, as was the case during the trial, no mortality or stroke benefit was observed in the group originally allocated to statins (Lloyd *et al*. 2013).

Cerebrovascular disease is increasingly common in older age groups and statin treatment has proven to be effective in reducing stroke risk in high-risk individuals in many RCTs (4S Study Group 1994, Lewis *et al*. 1998, HPS Collaborative Group 2002, Amarenco *et al*. 2006). However, existing evidence on stroke prevention among the elderly has been inconclusive (Teng *et al*. 2015, Hankey 2015). Evidence concerning the benefits of statins in heart failure patients is still lacking (Strandberg *et al*. 2014, Aronow

2015). Two trials among older heart failure patients have failed to show significant benefits from rosuvastatin compared to a placebo (Kjekshus *et al*. 2007, GISSI-HF Investigators, 2008).

In primary prevention or in low-risk older persons, evidence from treatment trials is scarce, only some subgroup analyses with "young-old" age groups are available (Sever *et al.* 2003, Ridker *et al.* 2008). The JUPITER trial was a primary prevention study comparing rosuvastatin to a placebo among apparently healthy individuals with elevated high-sensitivity CRP (Ridker *et al*. 2008). The trial reported such high rates of risk reduction of all major CVD events in the rosuvastatin treatment group (44%) that the ethical board decided to stop the trial after a follow-up of only 1.9 years. A subgroup analysis of 5695 persons aged 70 and older in the JUPITER trial revealed a 39% relative risk reduction in CVD events and large reductions in absolute event risks including the risk of ischemic strokes in the rosuvastatin group. The estimated 5-year NNT to prevent one major CVD event was 19 in the older subgroup compared to 29 in the younger subgroup (aged < 70) (Ridker *et al*. 2009).

Although several meta-analyses have been published during the last 10 years comprising all large statin trials, only few have specifically included trials with older persons (Ali *et al*. 2007, Roberts *et al.* 2007, Afilalo *et al*. 2008, Savarese *et al*. 2013) (Table 2.4).These meta-analyses have reported beneficial effects from statins mainly in secondary prevention populations, among individuals aged under 75. A recent meta-analysis (Savarese *et al*. 2013) evaluating the benefits of statins in elderly men and women at high risk but without established CVD, included 8 trials with a mean age of 73 years and a mean follow-up time of 3.5 years. The results indicate that statins compared to a placebo reduced the risk of MI by 39% (ARR 1.2% units; NNT 83) and the risk of stroke by 24% (ARR 0.7% units; NNT 143). Cardiovascular or all-cause mortality, however, were not significantly reduced. Cholesterol treatment trialists' (CTT) collaboration undertakes periodic meta-analyses of all relevant statin trials based on individual patient data on mortality and morbidity. Their meta-analysis based on data from 90,056 participants from 14 statin RCTs concluded that statin therapy can safely reduce the 5-year incidence of major CHD events, coronary revascularizations and stroke by about 20% per 1 mmol/l reduction in LDL-c, irrespective of a person's initial lipid profile, pre-existing diseases or age (Baigent *et al.* 2005). In the subanalysis of individuals aged > 65, the RRR for the combined endpoint was 19% and the estimated 5-year NNT was 27. A later CTT meta-analysis on low-risk populations also reported significant reductions in CVD events in a subgroup of over 70-year-old individuals (Mihaylova *et al*. 2012). However, reductions in mortality risks have not been reported in elderly subgroups.

Relevant observational studies on statin effects in the elderly are presented in Table 2.5. In a prospective follow-up study of a primary prevention cohort of elderly persons (Cardiovascular Health Study), statin use compared to non-use significantly decreased both the combined endpoint of MI, stroke and coronary death (risk 16.7 vs. 20.4%) and

all-cause mortality (Lemaitre *et al.* 2002). Similar results were received in the 75+ age group. Aronow and colleages have published several observational reports on the benefits of statins in different patient groups at risk for vascular events (Aronow 2015). In a study with 1410 older post-MI patients (mean age 81 years), 48% were treated with statins at discharge, and statin users had significantly fewer coronary events (50%), strokes (60%) or episodes with heart failure (48%) than non-users in a 3-year follow-up (Aronow *et al*. 2002). Similar benefits of statin use were reported by Allen Maycock *et al*. (2002) among a cohort of older CHD patients, even though, as noted, elderly persons were less likely to receive a statin prescription at hospital discharge than their younger counterparts. An observational register study followed a large cohort of post-MI patients aged ≥ 80 (*n* 14,907) and found that statin use at hospital discharge was associated with a reduction in all-cause mortality by 45% in the entire cohort and by 34% when the analysis was restricted to those who survived at least the first year (Gränsbo *et al*. 2010). It should be noted that only one quarter of the patients received statin treatment at discharge.

Petersen *et al.* (2010) reviewed 19 prospective observational studies, four RCTs and two observational treatment studies with participants aged 70 and older to evaluate the effects of statins in reducing mortality in the elderly. The authors concluded that there was insufficient trial evidence to confirm that statins reduce mortality in older persons without CVD. For individuals aged 80 or older with or without CVD, the evidence was insufficient to recommend anything regarding statin use.

A more recent study (Jacobs *et al*. 2013) observed a lack of association between cholesterol levels and mortality, yet treatment with statins was associated with reduced mortality in 85-90- year-olds in a 5-year follow-up. Similarly, in another recent report based on an analysis of the Three City Study primary prevention population aged 70 and older, baseline cholesterol values were not associated with mortality or any CVD outcome, but statin users had a decreased risk of ischemic stroke compared to non-users in a 9-year follow-up (Alperovitch *et al*. 2015). Surprisingly, no association was observed between statin use and coronary events. These results may, however, be confounded considering the observational nature of the study; statins may have been prescribed to and used by the healthier and less frail persons in the prospective cohort (see 2.6.3).

Many frail elderly people are dependent on daily assistance from other persons or live in a nursing home. No study has assessed the benefits (or risks) of statin treatment among such patient groups (Morley and Mahon 2013). Two observational studies, however, discovered that statin use was associated with reduced all-cause mortality among very old heart failure patients (Foody *et al.* 2006, Shah *et al.* 2008). Advanced renal failure and the undergoing of hemodialysis have been considered as surrogate for frailty. The AURORA study of hemodialysis patients detected no significant treatment effect for rosuvastatin in a follow-up of 3.8 years (Fellström *et al.* 2009).

2.6.3 Limitations of RCTs and observational studies in older persons

As presented in Table 2.3, older women have been underrepresented in most of the trials discussed above. RCTs typically consist of highly selected populations excluding the older, multimorbid, demented and frail individuals (Rothwell 2005, Konrat *et al*. 2012). Thus, the risk reductions achieved with statin treatment in RCTs will not necessarily translate into similar benefits among a much more heterogeneous group of older patients in reality. Furthermore, in practice, adherence to or persistence with the prescribed statin is often far from optimal in contrast to populations of RCTs who are being carefully and continuously monitored in their drug use (Osterberg and Plaschke 2005).

Observational studies have several weaknesses, especially when conducted in older populations. Selective prescribing of preventive drugs, such as statins, to those who either have a worse disease condition or, to those who have better general health status and longer life expectancy, may lead to a selection bias, as the health status is associated with CVD outcomes and mortality (Sedgwick 2014). The frail elderly are often not prescribed preventive medication. As an example of selection or a mortality bias, in the Three City Study, mortality in the non-statin user population was 13% higher when compared to the total cohort (Alperovitch *et al*. 2014). On the other hand, statins are recommended for high-risk patients irrespective of age; therefore, the CVD risk of statin users is likely to be higher than that of non-users, leading to higher event rates among statin users in observational cohorts, despite the risk reduction achieved by the treatment. This bias, confounding by indication (Rothman 2002, Brookhart *et al*. 2010) might explain the lack of risk reduction in coronary events in the Three City Study-cohort.

Table 2.3 Statin vs. placebo RCTs that included sufficient number of persons older than 70 years

RCT	Total cohort, n	Age (range), years	Male %	Follow-up years (mean)	Cardio-vascular risk level	RRR (%) of CVD-events/ all-cause mortality	Subanalysis of older persons[a], n	Age range	RRR (%) of CVD events/ all-cause mortality
CARE	4159	21-75	87	5.0	*high*	24/*NS*	1283	65-75	32/NR
LIPID	9014	31-75	83	6.0	*high*	29/22	3514	65-75	26/21
HPS	20,536	40-80	75	5.0	*high*	24/13	5806	70-80	18/13
PROSPER	5804	70-82	48	3.2	*high*	19/*NS*			
CORONA	5011	≥60	76	2.8	*high*(HF)	*NS*	2064	≥75	*NS*
ASCOT-LLA	10,305	40-79	81	3.3	*mod/ high*	36/NR	6570	>60	36/NR
CARDS	2838	40-75	68	3.9	*high*(DM)	37/*NS*	1129	65-75	38/*NS*
JUPITER	17,802	50-97	61	1.9	*low*	44/20	5695	≥70	39/20

RCT = randomized controlled trial; RRR = Relative risk reduction; CVD events = major cardiovascular events, including fatal events; *NS* = non-significant;NR = not reported; CHD = coronary heart disease; HF = heart failure;DM = diabetes mellitus; *high* = previous cardiovascular disease or diabetes; *mod/high* = no vascular disease but several risk factors (hypertension, smoking, diabetes, and/or dyslipidemia); *low* = apparently healthy persons

CARE = Cholesterol and recurrent events trial ([a]Lewis *et al*. 1998)
LIPID = Long-term intervention with pravastatin in ischemic disease study ([a]Hunt *et al.* 2001)
HPS = Heart Protection Study of cholesterol lowering with simvastatin in high-risk individuals ([a]HPS Collaborative Group 2002)
PROSPER = Pravastatin in the elderly at risk of vascular disease (Shepherd *et al.* 2002)
CORONA = Rosuvastatin in older patients with systolic heart failure. ([a]Kjekshus *et al.* 2007)
ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial-Lipid lowering arm ([a]Sever *et al*. 2003)
CARDS = Collaborative Atorvastatin Diabetes Study ([a]Neil *et al*. 2006)
JUPITER=Justification for the use of rosuvastatin in primary prevention ([a]Glynn *et al.* 2010)

Table 2.4 Meta-analyses of statin RCTs including older people (≥ 65 years)

Author	Number of trials included	Age (range), years	Follow-up years (mean)	Cardiovascular risk level	RRR with statin therapy (defined end-points)
Baigent *et al.* 2005	14 (subgroup)	> 65	5	mainly high risk persons	19% (major CVD events)
Roberts *et al.* 2007	5 (subgroup)	> 65 (12% were > 70)	5	high	17% (total mortality) 25% (MCE)
Afilalo *et al.* 2008	9	65-82	5	high	22% (total mortality) 30% (CHD death) 25% (stroke)
Brugts *et al.* 2009	6 (subgroup)	> 65	4	moderate/high (primary prevention)	*NS* for all end-points
Savarese *et al.* 2013	8	≥ 65, (mean 73)	3.5	moderate/high (primary prevention)	39% (MI) 24% (stroke) *NS* for mortality
Teng *et al.* 2015	8	≥ 65	3	low/moderate/high (primary prevention)	28% (CVD events) *NS* for stroke *NS* for total mortality

RCT = randomized controlled trial; RRR = relative risk reduction, MCE = major coronary events, *NS* = non significant; CVD = cardiovascular disease; CHD = coronary heart disease; MI = myocardial infarction

Table 2.5 Observational studies of statin use in older people

Author	Number of persons included	Age (range), years	Follow-up years (mean)	Cardiovascular risk level	RR or HR, users vs. non-users
Aronow and Ahn 2002	1410	60-100 (mean 81)	3.0	*high* (post MI)	0.5 (CHD events)
Allen Maycock *et al*. 2002	655	≥ 80	3.3	*high* (CHD)	0.5 (total mortality)
Foody *et al*. 2006	8452	≥ 80	3.0	*high* (post MI)	*NS* (total mortality)
Shah *et al.* 2008	3779	< 85	3.0	*high* (Heart failure)	0.73 (total mortality)
Cooke *et al*. 2009	4232	66-101 (mean 77.5)	2.3	*high* (CHD)	0.74 (total mortality)
Gränsbo *et al.* 2010	14,907	≥ 80	max 5 (median 0.8)	*high* (post MI)	0.55 (total mortality)
Olafsdottir *et al.* 2011	639 (subcohort with DM)	66-96 (mean 77)	5.3	*high* (DM)	0.47 (total mortality)
Jacobs *et al*. 2013	702	> 85	5	not reported	0.61 (total mortality)
Alperovitch *et al.* 2015	7484	74	9.1	mixed population	0.66 (stroke) *NS* (CHD events)

RR = relative risk; HR = hazard ratio; CHD = coronary heart disease; DM = diabetes mellitus; MI = myocardial infarction; *NS* = non-significant
high = previous cardiovascular disease or diabetes mellitus

2.6.4 Adverse effects

Large amounts of data exist not only on the efficacy but also on the safety of statin use. Statins are generally considered to be well-tolerated and safe (Bellosta and Corsini 2012). Adverse effects (AEs) associated with statin use are mostly mild and transient, including gastrointestinal problems, headache, sleep disturbances, allergic exzema, polyneuropathy or, most commonly, muscle symptoms (Banach *et al*. 2015). In addition, statin use may increase the risk of new-onset DM and this association is observed for different statins, indicating a class-effect (Stroes *et al.* 2015, Banach *et al*. 2015).

Statin-associated muscle symptoms include various muscle-related symptoms from mild myalgia or muscle weakness to actual myopathy with elevations of creatinine kinase (CK) over 10 times the upper normal limit, and, in rare cases, to life-threatening rhabdomyolysis (Stroes *et al*. 2015). Incidence of benign muscle symptoms ranges from 3-5% in RCTs to 10-20% in observational studies (Banach *et al*. 2015). Incidence rates of actual cases of myopathy have been 0.1−0.01% and those of rhabdomyolysis less than 0.01−0.001%, according to different reports (Banach *et al*. 2015, Stroes *et al*. 2015). Two large meta-analyses on statin safety did not find any significant difference in the incidence of rhabdomyolysis or high CK levels between statin treatment and placebo groups (Mills *et al*. 2011, Alberton *et al*, 2012).

Complaints of AEs are more common in observational studies than in RCTs owing to strict exclusion criteria of RCTs (Macedo *et al*. 2014). In a French study (PRIMO), 10.5% of patients receiving a high-dose statin treatment reported having muscle symptoms about one month after initiating the statin (Bruckert *et al*. 2005). Perceived adverse symptoms often lead to poor adherence to or discontinuation of the treatment. In an internet-based survey (USAGE) of over 10,000 former and current statin users, 29% of respondents had experienced some AEs and approximately two-thirds of the former users named AEs as the primary reason for discontinuation (Cohen *et al*. 2012).

Muscle-related AEs are in many cases dose-dependent (Stroes *et al*. 2015), and there are individual differences in tolerating statins deriving, in part, from genetic factors affecting liver metabolism. Interactions between statins and other drugs, especially those metabolized through liver cytochrome P450 isoenzyme CYP3A4, predispose a person to muscle symptoms (Magni *et al.* 2015). Simvastatin, atorvastatin and lovastatin are all metabolized by CYP3A4; thus, they are more prone to causing drug-drug interactions than pravastatin, fluvastatin or rosuvastatin, which use different metabolic pathways. Muscle symptomes may arise when a concomitantly used drug interacts with the statin metabolism, leading to increased statin exposure (plasma level). Common drug groups which have the potential to increase statin exposure are presented in Table 2.6. Cerivastatin was withdrawn from the market 2001 after an increased risk of rhabdomyolysis was associated with its use, most commonly in older women who concomitantly used cerivastatin and fibrates (Bhardwaj *et al*. 2013). Polymorphisms of the genes encoding statin transporter proteins and cytochromes may contribute to statin-

drug interactions and explain differences between individual patients' abilities to tolerate statins (Bellosta and Corsini 2012).

An approximately 9-12% increase in the incidence of type 2 DM across 3-5 years of statin treatment has been reported by several meta-analyses (Sattar *et al.* 2010, Mills *et al*. 2011, Preiss *et al.* 2011). Intensive-dose statins are more likely to induce new-onset DM than moderate-dose statins (Preiss *et al.* 2011), and, at present, the smallest risk has been linked to pravastatin (Navarese *et al*. 2013). Higher age during the statin treatment seems to increase the risk of developing DM (Sattar *et al*. 2010). In the 5-year post-trial follow-up of the original JUPITER study cohort, the DM risk had increased by 25% in the rosuvastatin treatment group compared to the placebo group. Of note, nearly all individuals who developed DM during the follow-up had evidence of impaired fasting glucose or metabolic syndrome already at the baseline. The absolute benefit of statin treatment on cardiovascular events was greater than the risk of developing DM (Ridker *et al*. 2012). The mechanisms by which statins influence glucose metabolism are still unclear, but several hypotheses of direct and indirect mechanisms exist. Statins may affect the insulin synthesis and excretion in the pancreatic beta-cells (Sattar and Taskinen 2012). Statins may also predispose to unintentional weight gain or by other mechanisms increase insulin resistance in the peripheral tissues (Vuorio *et al.* 2015). However, several scientists agree on the fact that the benefits of statin treatment on CVD events far exceed the risks of developing DM, especially for high-risk persons (Ridker *et al.* 2012, Banach *et al*. 2015).

Of all the relevant long-term statin trials, only the PROSPER trial (Shepherd *et al*. 2002) has reported increased cancer incidence in the statin treatment group compared to the placebo group, over a 4-year follow-up (HR 1.25, CI 1.04-1.51). However, in the 8.6-year post-trial follow-up based on record linkage, no such increased risk was observed (Lloyd *et al*. 2013). Large meta-analyses in this field have detected no evidence of increased cancer risk (Mills *et al*. 2011, CTT Collaborators 2012). The 15-year post-trial follow-up of the original WOSCOPS study group did not find increased cancer rates among the group that was treated with statins for 5 years during the study (McConnachie *et al.* 2014).

Mild elevations of liver transaminases have been described as being associated with statin use. However, in most cases this has had no clinical consequences (Banach *et al.* 2015). An increased risk of acute pancreatitis has been associated with statin use based on some observational data (Kuoppala *et al.* 2015), but the causality remains unclear. In contrast, a large meta-analysis of statin RCTs reported that the use of statins was associated with a lower risk of pancreatitis in patients with normal or mildly elevated trglyceride levels (Preiss *et al.* 2012). Increased risk of cataract has been linked to statin use in few reports (Leuschen *et al.* 2013). The findings of other studies have been inconsistent; some have even reported a decreased risk of cataracts in statin users (Dobrzynski and Kostis 2015).

2.6.5 Safety of statins in older persons

No trial has presented that older persons have more AEs from statins than younger ones. In the PROSPER study, discontinuations were equally common in the pravastatin treatment group as in the placebo group (Shepherd *et al*. 2002). A meta-analysis of statin trials in older adults reported no clinically relevant AEs, but mild musculoskeletal symptoms and mildly elevated levels of CK and liver transaminases were more common in the statin treatment group (Roberts *et al.* 2007). In general, when observed outside trial settings, older people are both more prone to drug-related AEs and more likely to experience nonspecific symptoms which may be incorrectly attributed to medication (Banach *et al*. 2015).

Aging causes changes in pharmacokinetics and pharmacodynamics, which affects the use of all medications, including statins. Pharmacokinetics, consisting of absorption, transportation, metabolism and finally elimination of the drug, is dependent on the individual's body composition, albumin level, liver function (metabolism) and renal function (elimination) (Bhardwaj *et al.* 2013). All these organ systems may be affected in old age. Prescribing statins to persons with renal insufficiency should be done with caution and high-intensity statins should be avoided (Stone *et al*. 2013). Many older people suffer from multiple comorbidities, thereby being susceptible to polypharmacy and drug-drug interactions. Statins that are not metabolized by CYP3A4 might therefore be safer for older people (Banach *et al*. 2015). Based on current evidence, statins seem to have neutral effect on cognition (Richardson *et al*. 2013, McGuinness *et al*. 2014, McGuinness *et al.* 2016). However, older individuals suffering from dementia are an extremely frail group of the elderly, and as such they are susceptible to AEs associated with statin as well as any other medication use (Huisman-Baron *et al*. 2011). Some observational reports exist in which statin use has negatively affected cognition (Evans and Colomb 2009) and the American Food and Drug administration (FDA) has stated that statin use "has a potential for reversible cognitive side effects such as memory loss and forgetfulness" (FDA, 2012). European guidelines on statin use have recommended use of lower doses at statin initiation for older persons, especially for frail individuals (Catapano *et al.* 2011).Table 2.6 illustrates factors associated with statin-related AEs in older persons.

Table 2.6 Factors associated with statin-related adverse effects in older persons (Bhardwaj *et al*. 2013, Magni *et al.* 2015, Banach *et al*. 2015)

*Female sex	*Treatment with interacting drugs:
*Frailty	*such as verapamil, amiodarone*,
*Small body size	*fibrates, macrolides, warfarin*,
*Hypothyreoidism	*diltiazem, azole antifungals*,
*Multiple comorbidities	*cyclosporine*
*Hepatic or renal dysfunction	*Concomitant use of grapefruit juice
*Vitamin D deficiency	*Excessive alcohol consumption

2.7 Dyslipidemia treatment guidelines

2.7.1 Finnish, European and US guidelines

Finnish Current Care guidelines on treatment of dyslipidemia were last updated in 2013 (Dyslipidemian Käypä hoito -suositus). The Finnish population-level recommendations for the treatment of dyslipidemia to prevent CVD are illustrated in Figure 2.3. The guidelines recommend, in parallel with lifestyle changes, the use of statin treatment for all high or very high risk individuals referring to people with existing CVD or equivalent high risk conditions. For all other people, evaluation of the total cardiovascular risk is recommended.

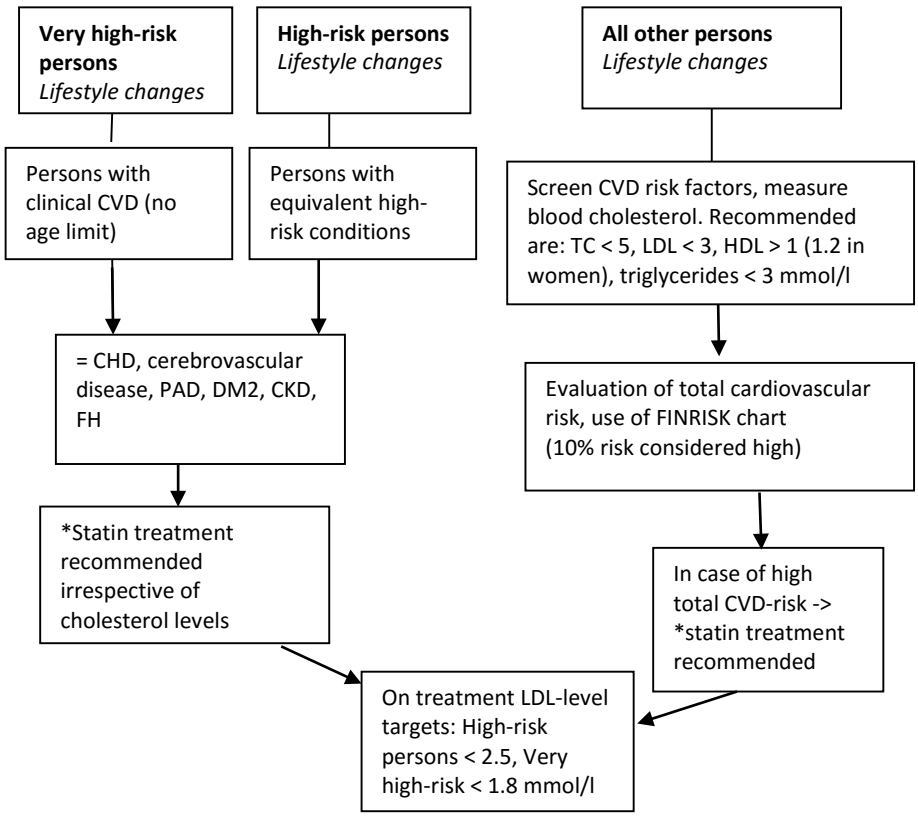

Figure 2.3 Finnish recommendations for the treatment of dyslipidemia.

CVD = cardiovascular disease; CHD = coronary heart diasease, PAD = peripheral artery disease; DM2 = type 2 diabetes mellitus, CKD = chronic kidney disease, FH = familial hypercholesterolemia; FINRISK = risk estimation chart based on Finnish population surveys

The European guidelines on the treatment of dyslipidemia recommend statin treatment for all very high-risk and high-risk individuals, matching the Finnish guidelines (European guidelines for treatment of dyslipidemia, Catapano *et al*. 2011). For all other people, use of the Systematic coronary risk evaluation chart (SCORE) for the total CVD risk estimation is recommended. Treatment with statins is recommended for secondary prevention in the same way for persons aged over 65 as for younger ones. In addition, treatment with statins should be considered for those older persons without CVD but with at least one cardiovascular risk factor apart from age. However, clinical judgement is warranted.

The most recently updated dyslipidemia treatment guidelines are the American guidelines (American College of Cardiology-American Heart Association Task Force on Practice Guidelines, Stone *et al*. 2014). These guidelines also emphasize the total cardiovascular risk assessment when making treatment decisions. In addition, the guidelines practically eliminate LDL goals as a treatment target, which has raised discussion worldwide. The American guidelines also identify patient groups for whom the guidelines are not suited for. They exclude patients with heart failure (NYHA classes II-IV) and those with end-stage renal disease (hemodialysis patients), since the available data do not support statin use in these patient groups. In addition, no recommendation (for statin use) is given for patients over 75 years old without existing CVD due to the lack of trial data. The guidelines also differentiate between moderate and high-intensity statin treatment and recommend using moderate-intensity treatment for patients predisposed to statin AEs, including all the persons over 75 years of age.

2.7.2 Risk calculators for estimating cardiovascular event risk

Total cardiovascular risk calculators or charts are designed for the purpose of facilitating the estimation of CVD risk in apparently healthy persons who have no signs of clinical CVD (Bitton and Gaziano 2010). The FINRISK chart is based on a 10-year follow-up of Finnish population samples from different areas aged 30 to 64 (Vartiainen *et al.* 2010). Risk factors included are: age, sex, smoking, BP, DM, TC and HDL-c levels and family history of MI. Based on individual risk factors present, the chart calculates an estimated risk of developing a fatal or nonfatal CVD event during the next 10 years. Statin treatment is recommended to all individuals with ≥ 15% risk (=very high risk) or ≥ 10% risk (= high risk) in the FINRISK calculator (Finnish Dyslipidemia Current Care guidelines 2013).

The SCORE chart (Conroy *et al*. 2003) is based on large, representative European cohort data sets, derived from long-term prospective studies. It predicts the 10-year risk of a fatal CVD event and is validated up to the age of 65. A 5% risk of CVD death is considered high and can be converted to a 15% risk of a CVD event. It originally included all the traditional risk factors (excluding DM); HDL-c and BMI-values have been added later. A 5% risk of fatal CVD in the SCORE chart would be comparable to a 10% CVD event risk estimated by the FINRISK chart (Vartiainen *et al*. 2010).

In the new American guidelines, the estimated 10-year risk of atherosclerotic CVD is calculated with the pooled cohort equation (Stone *et al*. 2013). This risk calculator is based on pooled data derived from several large cohort studies, but the calculator itself has not been prospectively tested for its accuracy in predicting the risk and has been criticized for overestimating the risks in some populations (Keaney *et al*. 2014).

All three risk calculators presented here are likely to overestimate the CVD risk when used for the elderly, aged > 70. For example, the American pooled cohort risk calculator always estimates an increased or high 10-year risk in men aged > 66 and women aged > 70 years, even if no other risk factors are present. According to this, all older people would be recommended to use statins for CVD prevention. When the FINRISK chart was tested among 60-74 year-olds in a cross-sectional population survey in 2007, the high-risk limit was exceeded by 87% of all men and by 32% of all women (Vartiainen *et al.* 2013). Thus, the use of risk calculators that are based on population studies consisting of mainly middle-aged populations is questionable with older people.

2.8 Pharmacoepidemiology of statins

Pharmacoepidemiologic studies complement the data derived from clinical treatment trials and offer the possibility of studying usage patterns and effectiveness of drugs in real-life patients. Furthermore, valuable data on the safety of new drugs coming to the market can be acquired from these studies as they are conducted in large populations and are in many cases based on national health databases (Strom 2002).

2.8.1 Trends in statin use among older persons

The first statin, lovastatin came to the global market in 1987. Over the following decades, statin use has increased worldwide, and statins have become the most widely prescribed drug class in the history of medicine (Kastelein 2014). The growth in the use of statins has also been fast among older persons. In 2010, a review estimated that one-third of older Europeans (aged 75-84) were currently treated with statins (Petersen *et al.* 2010). According to register studies from various countries, statin use has expanded widely not only among older CHD patients but also among the primary prevention population (Geleedst-De Vooght *et al.* 2010, Robinson and Booth 2010, Wallach Kildemoes *et al.* 2012). In Denmark, a nationwide register study followed trends in statin use over the period 1996-2009 and observed a shift toward primary prevention and an increasing prevalence of statin use among persons 75 and older (Wallach Kildemoes *et al*. 2012). In Sweden, every third person in the age group of 75-84 years purchased statins in 2008 (Silwer *et al.* 2008). A register study on trends of statin use among the total Finnish population (Ruokoniemi *et al*. 2008) observed an 11-fold increase in the prevalence of statin use from 1995 to 2005, and a clear shift towards older age groups. According to the Finnish Medicines Agency statistics (FIMEA, 2011), 474,544 people purchased statins in 2005 and 680,611 people in 2010, indicating over 40% growth in the number of statin users nationwide.

Despite the overall increasing prevalence figures, underuse or underprescribing of statins has been commonly observed among the older age groups. Among the elderly MI survivors in the United States, the use of statins increased from 11% to 61% from 1995-2004. However, patients in older age groups were significantly less likely to receive statins (Setoguchi *et al.* 2007). Similarly, in the cross-sectional National Health and Nutrition Examination Surveys from 2001 to 2006, statin use increased in all age groups, especially in secondary prevention populations (Robinson and Booth 2010). However, individuals over the age of 75 (with or without CVD) were less likely to use statins. A consistent underuse of evidence-based therapies (including statins) has been observed in the older age groups (Åsberg *et al*. 2010, Candrilli *et al*. 2010, Gränsbo *et al*. 2010). According to the studies, several reasons may contribute to this, such as safety and efficacy concerns, lack of trial data, differences between "young olds" (65-75), "olds" (75-85) and "old-olds" (over 85), substantial heterogeneity among the elders independent of age, higher prevalence of polypharmacy and comorbidities, cost-effectiveness concerns (lack of evidence), perceived short life expectancy and poor adherence to prescribed therapies (Hamilton-Craig *et al*. 2015).

2.8.2 Statin reimbursement rules as drivers for statin use in Finland

According to the Finnish drug insurance scheme run by the Social Insurance Institution (SII), an individual pays a minimum deductible per statin purchase, and the rest of the price is partially reimbursed. The basic reimbursement was 42% of the price of the drug until 2012 and lowered to 35% thereafter (FIMEA 2013). However, individuals with specific, chronic conditions receive a higher percentage of the price refunded than those who buy the same drug without having these conditions. This is called the special reimbursement which may be either 100% (higher special reimbursement) or 65% (lower special reimbursement), depending on the specific condition of the individual. To be eligible for special reimbursement, a person's condition must meet explicit predefined criteria and a written certificate is required from the treating physician. For example, individuals diagnosed with FH or CHD are entitled to a special reimbursement for their statin purchases, and DM patients for their purchases of antidiabetics. The Special Refund Entitlement Register held by the SII keeps records of all the persons who receive special reimbursement for some drug treatments (Furu *et al*. 2010).

During the statin era, there have been several changes in the prices and the reimbursement rules of statins available on the market, which has influenced statin use trends, along with the increasing trial evidence and publications of treatment guidelines. (Table 2.7). In Finland, generic simvastatin preparations were introduced onto the market in 2003, which gave rise to more competition and lower out-of-pocket costs. In 2006, the drug reimbursement policy changed, after which the more expensive statins (atorvastatin and rosuvastatin) could only be reimbursed if a trial with less expensive statins had failed (Martikainen *et al.* 2010). Simvastatin has been the most widely used statin in Finland since 2003, at least partly owing to the lower cost for the patients (Finnish Social Insurance Institution Statistical Database). Generic atorvastatin was introduced in 2009 and rosuvastatin in 2010, and since then there have been generic low-price substitutes for all statins on the Finnish market.

Table 2.7 Land-mark statin trials, treatment guidelines and health care policies as drivers for statin use in Finland

Time period	**Clinical trial evidence** RCTs, meta-analyses, observational studies	**International guidelines on use of statins**	**Finnish guidelines on CVD prevention and treatment of dyslipidemia**	**Finnish Health care policies and statin reimbursement rules**
1990-1999	**Secondary prevention** 1994: 4S, efficacy of statins in middle-aged MI/CHD patients with hypercholesterolemia 1996-1999, CARE, LIPID: similar benefits	1994: 1st European Task Force on CHD prevention, total cholesterol target < 6 mmol/l 1998: 2nd European Task Force on CHD prevention, LDL target <3mmol/l	1996: Suomen sisätautilääkärien yhdistys *et al.* recommendations for prevention of CHD in clinical practice.	1988: first statin introduced, lovastatin 1992: higher reimbursement in FH 1992: simvastatin, pravastatin 1997: atorvastatin 1998: fluvastatin
2000-2003	2002: HPS, efficacy in CHD, DM, cerebrovascular disease, PAD irrespective of age or lipid levels 2002: PROSPER, efficacy in older persons at high risk 2003: ASCOT, efficacy in persons free of CHD but with other risk factors	2001: 3rd American NCEP ATP III guidelines: DM is CHD-equivalent high-risk condition, LDL targets, < 2.5mmol/l 2003: 3rd European Joint Task Force on CVD prevention: broadening of indications, introducing SCORE chart	no guidelines 2003: publication of the FINRISK Study, risk factors for CVDs in Finnish population, (Vartiainen *et al.*); in the Finnish Medical Journal several publications promoting the use of inexpensive statins	2000: higher reimbursement for persons with dyslipidemia associated with CHD 2003: generic substitution of simvastatin-> more competition 2003: rosuvastatin introduced
2003-2006	2004: CARDS, efficacy in DM 2005: TNT, treatment targets should be lower	2006: ACC-AHA guidelines for the secondary prevention of coronary and other atherosclerotic vascular disease: LDL-c treatment targets lower, <1.8 mmol/l	2004: Joint Finnish Task Force for the Finnish Current Care guidelines for the treatment of dyslipidemia: high-risk groups identified , treatment target levels (LDL <2.5 in high risk), use of the SCORE chart in total risk estimation	simvastatin use increases, 2005: some generic simvastatin products so cheap that they fall below the deductible limit
2005-2008	Meta-analyses 2005: CTT trialists, Efficacy of statins in wide patient groups irrespective of age and lipid levels 2007-2008:Meta-analyses in high risk older persons	2007: The 4th European Joint Task Force guidelines on CVD prevention: lower cholesterol treatment targets	2008: European guidelines (4th Joint Task Force) on CVD prevention published in Finnish in the Finnish Medical Journal and implemented into clinical practice guidelines	2006: change in reimbursement policy,more expensive statins reimbursable only after trials with cheaper ones have failed-> many switched to simvastatin from atorvastatin and rosuvastatin
	(*continued*)			

Time period	**Clinical trial evidence** RCTs, meta-analyses, observational studies	**International guidelines on use of statins**	**Finnish guidelines on CVD prevention and treatment of dyslipidemia**	**Finnish Health care policies and statin reimbursement rules**
2009-2013	**Primary prevention** 2009: JUPITER, efficacy in apparently healthy persons 2011, 2013:Cochrane reviews, efficacy in primary prevention 2010, 2012: CTT trialists meta-analyses: efficacy in low risk populations, also > 70 years	2011: European ESC/EAS Guidelines for the management of dyslipidemia 2012: 5th European Joint Task Force for CVD prevention 2013:ACC-AHA updated cholesterol treatment guidelines: no- LDL thresholds, estimation of total CVD-risk, persons ≥ 75->no recommendation in primary prevention	2009: updates of the Finnish Current Care guidelines for dyslipidemia:total risk assessment in asymptomatic persons with the FINRISK-chart 2013: Last update of the Current Care Guidelines for dyslipidemia: high and very high risk groups identified, LDL-targets set to < 2.5 and < 1.8 mmol/l, respectively; new risk groups included: advanced CKD	2009: reference price-system introduced ->lower out-of-pocket prices for all prescription drugs 2009: generic atorvastatin 2010: generic rosuvastatin Generic substitution available for all statins in the market

RCT = randomized controlled trial; CVD = cardiovascular disease; CHD = coronary heart disease; MI = myocardial infarction; DM = diabetes mellitus; CKD= chronic kidney disease; PAD = peripheral artery disease; SCORE = systematic coronary risk estimation-chart; FINRISK = risk chart for estimation cardiovascular event risk (based on FINRISK-population surveys); FH = familial hypercholesterolemia

Guidelines:

Suomen sisätautilääkärien yhdistyksen työryhmä. Sepelvaltimotaudin ehkäisy käytännön lääkärin työssä. (Suomen Sisätautilääkärien Yhdistyksen työryhmä 1996)

Finnish Dyslipidemia Current Care Guidelines (Käypä hoito - suositus): Updates 2004, 2009, 2013

European Society of Cardiology (ESC) and Other Societies Guidelines on CVD prevention: 1st, 2nd, 3rd, 4th, 5th Joint Task Force (last Update Perk *et al* 2012);

European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) Task Force for the management of dyslipidemias (Catapano *et al.* 2011)

National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report (NCEP Expert Panel ATP III 2001)

American College of Cardiology (ACC)-American Heart Association (AHA) Guidelines for Secondary Prevention for Patients with Coronary or Other Atherosclerotic Vascular disease: 2006 Update. Endorsed by the National Heart, Lung and Blood Institute (Smith *et al*. 2006)

American College of Cardiology (ACC)-American Heart Association (AHA) Task Force Guidelines on the Treatment of High Blood Cholesterol to reduce Atherosclerotic Cardiovascular Risk in Adults(Stone *et al*. 2013)

Trials:

4S (4S Study Group. 1994), CARE (Lewis *et al*. 1998), LIPID (LIPID Study Group 1998), HPS (HPS Collaboration 2002), PROSPER (Shepherd *et al*. 2002), ASCOT (Sever *et al*. 2003), CARDS (Colhoun *et al.* 2004), TNT (LaRosa *et al*. 2005), JUPITER (Ridker *et al*. 2008)

Meta-analyses:

Cholesterol Treatment Trialists (CTT) Collaboration (Baigent *et al*. 2005, Mihailova *et al*. 2012); Roberts *et al*. 2007, Afilalo *et al*. 2008)

2.8.3 Persistence and adherence of statin use

Persistence with prescribed medication can be defined as the overall duration of the treatment, whereas, according to a new taxonomy (Vrijens *et al.* 2012) medication *adherence* is a broader term consisting of the whole process by which the patients take their medication as prescribed. Adherence has three components: initiation, implementation and discontinuation. The process starts with the initiation of the prescribed drug therapy, and discontinuation is the end of the therapy. Persistence is the length of time between the initiation and discontinuation. Thus, low or poor adherence occurs when the patient does not begin to take the medicine at the right time or at all, when the dosing taken by the patient does not correspond to the prescribed dosing (for example the patient takes only 1 pill /a day instead of the prescribed 2 pills), or when the treatment is discontinued early.

In most drug utilization studies adherence is defined as consuming < or ≥ 80% of the prescribed medication, less than 80% meaning "poor" adherence and 80% or more "good" adherence (Chowdhury *et al*. 2013). Typically, in studies based on pharmacy (claims) records, medication possession ratio (MPR) or the proportion of days covered (PDC) is calculated based on the number of pills dispensed at each pharmacy transaction during a specific period of time (Andrade *et al*. 2006). When measuring the persistence, defined as the time from initiation to discontinuation the gap method is often used (Andrade *et al*. 2006). Gaps are periods in which no medication is available to the patient, the maximum gap being the number of days that are allowed between two consecutive prescriptions (or statin purchases). If the pre-defined gap period is exceeded, the treatment is considered discontinued. Minimum gap lengths of 60, 90, 180 or 270 days have been used in studies (Helin-Salmivaara *et al*. 2008, Caspard *et al*. 2005). Some studies have used different gap lengths as sensitivity analyses and typically longer gaps have yielded higher persistence rates (Geers *et al.* 2011). This thesis presents the results from a persistence study where the "anniversary" method was used to measure the persistence of statin use allowing a maximum of 365 days between two statin purchases.

In the past decades, many studies have addressed this important issue. It has been difficult to compare the results of the adherence studies due to the inconsistency of the terminology and methods used (Vrijens *et al*. 2012). However, adherence with preventive medications is shown to be far from optimal (Osterberg and Blatschke 2005, Caspard *et al*. 2005, Chowdhury *et al.* 2013). In an Australian register study almost half of the persons who were prescribed statins discontinued the treatment for various reasons during the first six months (Simons *et al*. 2011). Many of the discontinuers, however, restart statin use sometime later (Korhonen *et al.* 2011, Zhang *et al.* 2013). In a Finnish nationwide register study, 48% of the 32,760 persons who had newly initiated statin use had discontinued it at some point for at least 180 days by the end of the study (10-year follow-up from 1997 to 2007) (Korhonen *et al.* 2011). Of the discontinuers, nearly 50% restarted the treatment within one year, and nearly 90% restarted by the end of the follow-up.

Those adherence studies that have included a substantial number of older persons (> 65 years) have, in general, found poor adherence or persistence rates, ranging from 34% to 74% for 1-year persistence and from 26% to 65% for 5-year persistence (Table 2.8). Several reasons have been identified as being associated with discontinuation or poor adherence of statin use, such as older age or younger age (the middle-aged being the most adherent), female sex, lower income, or primary prevention indication for statin use (Caspard *et al.* 2005, Mann *et al*. 2010, Lemstra *et al*. 2012). New statin users (initiators) are more likely to discontinue the use than long-time prevalent users (Lemstra *et al*. 2012). Adherence is related to the individual's perceived cardiovascular event risk; consequently, those with a history of CVD, diabetes or hypertension have been demonstrated to be more adherent users than those without these diseases (Helin-Salmivaara *et al* 2008, Mann *et al*. 2010, Lemstra *et al*. 2012).

Poor adherence to statin treatment has been associated with worse clinical outcome (Shalev *et al.* 2012, Chowdhury *et al*. 2013), increased rate of hospitalization and even higher mortality (Liberopoulos *et al*. 2008). The discontinuation of prescribed statin treatment soon after a CVD event (MI or stroke) may increase the risk of a new event and mortality (Colivicci *et al.* 2007, Allonen *et al*. 2012). A recent Finnish adherence study on diabetes patients initiating statins reported that good adherence was associated with a 23% decrease in the incidence of ischemic stroke compared to poor adherence (Korhonen *et al*, 2015). Moreover, it has been suggested that statin withdrawal may even lead to a worse clinical outcome in high-risk individuals when compared to not initiating statin treatment at all (Gomez Sandoval *et al*. 2011, Liberapoulos *et al*. 2008).

Table 2.8 Statin adherence studies containing older persons

Study number	Age-range (years)	Design	Follow-up	Patient characteristics	Adherence defined as	Adherence rates
Benner *et al*. 2002 n=34501	≥ 65	new users (18 months no statin)	5 years	45% had CHD	PDC ≥ 80% assessed every 6 months	26%
Jackevicius *et al*. 2002 n=143,505	≥ 66	new users (12 months no statin)	2 years	1:ACS 2:chronic CHD 3:no CHD	gap 120 days	1:40% 2:36% 3:25%
Caspard *et al.* 2005 n=4776	adults, 60% > 60	new users (no previous statin use)	3 years	usual care setting	PDC ≥ 80% gap < 183 days	61% persistent; (51% with good adherence)
Kulkarni *et al*. 2006 n=1326	adults, mean 65.7	statin users at hospital discharge	1 year	CHD, post-angiography	self-report	72% persistent
Hudson *et al*. 2007 n=34735	mean 71	hospital discharge register	5 years	post MI	gap 60 days	65%
Rasmussen *et al*. 2007 n=17 823	≥ 66	statin users at hospital discharge	2.4 years	post MI	PDC ≥ 80% gap 180 days	87% persistent
Schneeweiss *et al*. 2007 n=12545	≥ 66	new users (6 months no statin)	1 year	baseline cohort of statin initiators	PDC > 80% gap 90 days	60%
Helin-Salmivaara *et al*. 2008 n=18072	adults, 40% ≥ 65	new users (12 months no statin)	10 years	nationwide cohort based on drug reimbursement register	PDC ≥ 80% gap 270 days	44%
Chapman *et al.* 2008 n=8406	adults, 50% ≥ 65	new users (12 months no use)	1 year	Concomitant therapy with antihypertensives and statins	PDC ≥ 80% assessed at 3-month intervals	36% adherent with both drugs
Simons *et al*. 2011 n=77867	adults 65% ≥ 65	new users (6 months no statin)	variable (max 5 years)	nationwide cohort based on pharmacy claims register	Gap 90 days	11-month median persistence time
Warren *et al*. 2013 n=58602	≥ 45	long-term (prevalent) users	2 years	1:Concession card holders[a] 2:General beneficiaries[b]	MPR ≥ 80% during a 24-month period	1: 80% 2: 57%

ACS = acute coronary syndrome; CHD = coronary heart disease; MI = myocardial infarction;
PDC = proportion of days covered; MPR = medication possession ratio; gap =the number of days allowed between two consecutive prescriptions (or refills)
[a] received a higher refund of the statin price,[b]higher out-of-pocket costs for statins

2.9 Rationale for this study

The association of cholesterol levels with cardiovascular and all-cause mortality in older persons has been described by several previous reports with somewhat inconsistent conclusions. In this thesis, we describe mortality associations and age-related changes of cholesterol levels in older persons examined in the pre-statin era. Furthermore, remarkable declines in the CVD risk factors during the past decades have resulted in significant decreases in mortality and morbidity of CVDs in Finland, especially among the middle-aged population (Vartiainen *et al*. 2010). Whether the trends observed in the cholesterol values and CVD morbidity of the middle-aged Finnish population reflect those of the older population is one of the questions this study aims to address.

During the 2000s in Finland, statin use increased remarkably, also in older age-groups. The two register studies of this thesis were designed to clarify statin usage patterns, to discover whether statin use among the older population is following the national guidelines, and determine how well older people actually persist with the prescribed statin treatment.

3 AIMS OF THE STUDY

The purpose of this thesis was to study the association of cholesterol levels with CVD and mortality in older persons. Furthermore, this study aimed to describe changes in the statin use and CVD risk profiles of older Finns. The specific aims of the five studies included in this thesis were as follows:

Study I	to examine the association of cholesterol levels with total and CVD mortality in a 12-year follow-up of 70-year-old Finns
Study II	to describe longitudinal changes in cholesterol levels of 70-year-olds in a 15-year follow-up
Study III	to describe and compare CVD risk profiles and use of preventive medications (focus on statin use) in two 70-year-old cohorts examined 20 years apart
Study IV	to describe population level trends in the prevalence and incidence of statin use and the channeling of statin use according to individual CVD risk status among Finns aged 70 and older
Study V	to characterize new statin users in terms of CVD morbidity and risk profiles and to investigate the persistence of statin use among Finns aged 70 and older

4 MATERIALS AND METHODS

(The design and study populations of the five substudies are presented in Table 4.1.)

4.1 Cohort studies (Studies I, II, III)

4.1.1 Design and study populations

The study populations, comprising 70-year-old residents of the city of Turku, were derived from two birth cohorts, those born in 1920 and, for the later study, those born in 1940. Initially, a prospective cohort study, the Turku Elderly Study (Turun vanhustutkimus, TUVA) was launched in 1990, and originally all 1920-born residents of Turku (n= 1503) were invited to participate in the study (Figure 4.1). Of the eligible participants, those who lived in long-term care facilities, such as nursing homes were excluded. Finally, 1032 persons, almost 80% of all home-dwelling 70-year-old Turku residents participated in the study. Baseline examinations took place in the Turku City Hospital in 1991-1992. This original cohort of 1032 was followed-up for mortality and morbidity for 20 years, with follow-up examinations similar to the baseline protocol taking place 10 years, 15 years and finally 20 years after the baseline examination.

In Study I, subjects with dementia (n=80) and those with missing values in their lipid or risk factor panels (n=75) were excluded from the baseline TUVA cohort, leaving 877 subjects eligible for the analyses. The population in Study II is also derived from the same original cohort of 1032, although excluding those subjects who used lipid-lowering medication or had missing values in their lipid panel in one of the three examinations. Lipid measurements from the baseline examination (n=956), first follow-up examination (n=492) and second follow-up examination (n=221) were used for the analysis.

The second birth cohort, born in 1940, was invited to participate in the New Turku Elderly Study (Uusi Turun vanhustutkimus, UTUVA) 20 years later, in 2010. Of the 1344 eligible 70-year-olds, 1307 home-dwelling individuals were invited and, of them 956 (73%) participated the study (Figure 4.1). In Study III, baseline characteristics including cardiovascular morbidity, risk factors and preventive medication use (focus on statins) of the two cohorts were described and compared.

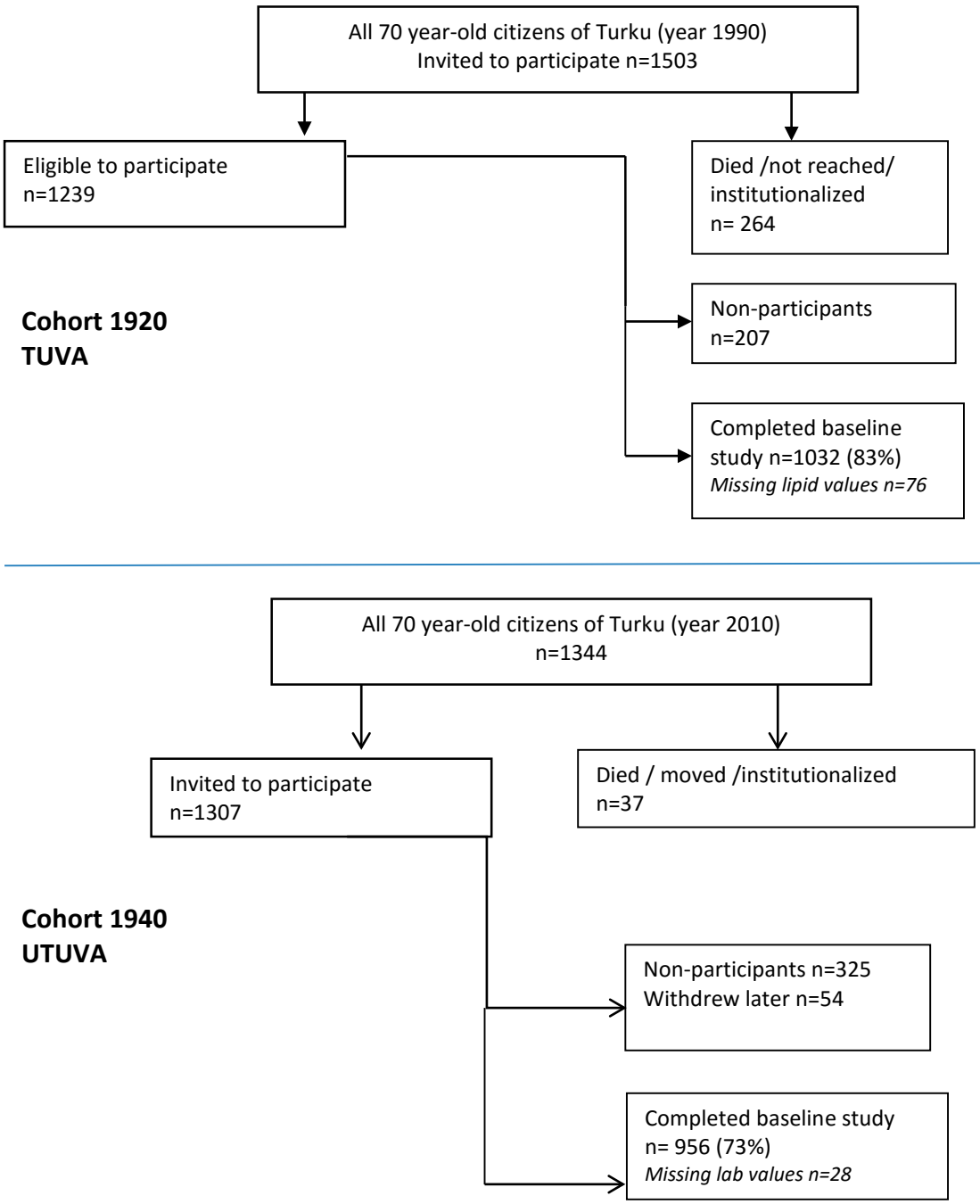

Figure 4.1 Study population of the cohort studies (I, II, III)

4.1.2 Data collection

Both the TUVA and UTUVA study cohorts underwent the same protocol of examinations at baseline. First, a mailed survey was filled out by the participants. The survey was then thoroughly rechecked together with the study nurse and the physicians. The participants' medical history, including medication use, previous diseases and operations as well as their lifestyle habits, functional abilities and social data on living conditions etc. were gathered by the survey. Their history of DM, hypertension, CHD, PAD, stroke and cancer was recorded, as well as previous and current smoking habits and alcohol consumption. Mini Mental State Examinations were performed and those who scored < 24 points were referred for further evaluation of cognitive functions. A comprehensive physical examination was performed by study nurses and physicians with systematic examinations of all basic organ systems. Physical performance testing was also performed. The laboratory examinations were carried out after a 12-hour overnight fast. The plasma levels of cholesterol (TC, LDL-c, HDL-c, triglycerides) and glucose were determined. Other, additional, laboratory parameters were also determined but they are irrelevant to this study. The electrocardiogram (ECG) and BP were measured. The body mass index (BMI) was calculated afterwards, based on measured weight and reported height (kg/m^2). The study physicians (several in TUVA and a single one in UTUVA) had access to all previous patient records from the local health care facilities as well as results from past and current laboratory examinations.

The data gathered from the surveys, including laboratory results and physician-confirmed diagnoses were saved in a common database. The laboratory measurement method of serum lipids was changed between the old and the new study, which may have influenced the lipid values. Specifically, the HDL-c measuring method changed from the polyethylene glycol precipitation method to a direct enzymatic method, resulting in approximately 5% higher HDL-c values in the new cohort (personal communication). This difference has been accounted for in the results. Medications used in both cohorts were later classified according to the specific Anatomic Therapeutic Chemical (ATC) classification system (2010 revision).

The death certificates of participants of the TUVA cohort since baseline have been retrieved from the Statistics Finland, and specific causes of death (the underlying causes of death) have been reviewed and classified according to ICD-9 until Dec. 31, 1995 and according to ICD-10 thereafter. The diagnoses of CHD, cerebrovascular disease, congestive heart failure, peripheral artery disease or atherosclerosis universalis were classified as cardiovascular mortality.

4.1.3 Data analysis and outcomes in Study I and II

The association of the baseline levels of TC, LDL-c, HDL-c and triglycerides with cardiovascular and all-cause mortality was originally assessed in a 12-year follow-up, as published in Study I. Additionally, 15- and 20-year mortality follow-ups of the same cohort were performed for this thesis. Analyses were carried out after stratifying the subjects into four groups according to the levels of each measured lipid fraction. Univariate analyses were performed separately for each lipid fraction by using cross-tabulations and calculating risk ratios (RRs) of death, with 95% confidence intervals. The analyses were performed for men and women separately and, additionally, for both sexes combined. The association between the lipid levels and mortality was further estimated with multivariable Cox proportional hazards models, adjusting for the following confounding variables: gender, BMI, smoking history, previous CHD, stroke, DM and hypertension. History of cancer was included as a covariate in the model for all-cause mortality but not in the model for CVD mortality.

The second study was also based on the lipid values of the TUVA cohort. The measurements of TC, LDL-c, HDL-c and triglycerides at baseline, first follow-up and second follow-up examination were used for this analysis. All mean lipid values in the three examinations were reported stratified by sex. The main outcome in this study was the longitudinal changes in the lipid values of those subjects who participated in all three examinations (n= 221). Changes in the lipid values between baseline and follow-up examinations were calculated as a 10-year and 15-year change. Variance analysis was used to assess the statistical significance of the changes over time and differences between the sexes. In multiple regression models, the observed lipid changes were adjusted for sex, CHD, cancer, smoking history, alcohol use status and with changes of BMI, serum creatinine level and physical performance, also measured at each examination.

4.1.4 Definition of variables and data analysis in Study III

The baseline prevalences of CVDs, cardiovascular risk factors and medication use in both TUVA and UTUVA cohorts were calculated and compared. Prevalences of the following CVDs were presented: CHD, ischemic stroke/TIA, PAD and DM (considered a CVD equivalent). The prevalence of cardiovascular risk factors, such as hypertension, dyslipidemia, smoking, and the mean BMI, fasting glucose and cholesterol values were presented for both cohorts. The use of any medication, statins (ATC code C10AA), antidiabetics (A10), antihypertensives and cardiovascular medication was presented for both cohorts. Cardiovascular medication included all medications used for different CVDs (except statins and antithrombotics): nitrates and cardiac glycosides (C01), miscellaneous cardiovascular drugs (C02), diuretics (C03), beta-adrenoceptor blockers (C07), calcium antagonists (C08), angiotensin-converting-enzyme inhibitors and angiotensin II-receptor blockers (C09). Antihypertensives included all the above groups of cardiovascular medications, except C01.

The populations of both cohorts were further classified into three mutually exclusive cardiovascular risk groups based on the presence of CVDs and risk factors: low, moderate and high-risk groups. 1) The *high-risk group* consisted of persons who had received one or several of the following diagnoses: CHD, stroke/TIA, PAD and DM. 2) The *moderate-risk group* consisted of those free of CVD and DM, but with hypertension and/or any cardiovascular medication use. 3) The *low-risk group* consisted of those free of CVD, DM and hypertension who did not use any cardiovascular medication. In addition, in the 1940 cohort, the proportions of persons in the three risk groups were calculated stratified by the use of statins.

For statistical analyses, the Chi-Square and Fisher's exact test were used for comparing the differences in the proportions between the groups. Variance analysis was used for comparison of the means of lipid, glucose, BMI and BP levels.

Table 4.1 The design and study populations of the 5 substudies

	Study I	Study II	Study III	Study IV	Study V
Study design	prospective cohort study	prospective cohort study	cross sectional cohort comparison	(longitudinal) register study	(longitudinal) register study
Study population	residents of Turku born in 1920 who were home-dwelling in 1990	the same as in Study I, but *excluding* subjects using statins and subjects with missing values	residents of Turku born in 1920 and 1940 who were home-dwelling in 1990 and 2010, respectively	the total home-dwelling Finnish population aged ≥70 in 2000–2008	the total home-dwelling Finnish population aged ≥70 who started statin use in 2000–2008
Number	1032	956	1032; 956	883,051	157,709
Female %	64	64	64; 59	61-64	56-65
Age range	70-71	70-71	70-71	≥70	≥70
Study years	1991	1991/2001/2006	1991 and 2011	2000–2008	2000–2008
Follow-up	12 years	15 years	Not Applicable	9 years	9 years

4.2 Register studies (studies IV and V)

4.2.1 Design and study populations

The study population for Study IV comprised all Finnish inhabitants aged 70 years and older in 2000−2008 (n= 883,051). The study population was dynamic: each study year new people turning 70 were included, and those who died were excluded. In addition, those institutionalized for longer than 90 days during a calendar year were excluded from the study population, since their statin use could not be tracked by the purchases registered in the national Prescription Register. During the nine-year period from 2000 to 2008, the number of non-institutionalized Finns aged ≥ 70 years increased from 456,867 to 538,492. In Study V, only those in the above described study population who initiated statin use during the nine-year period (without any registered statin purchases in the preceeding three years) were identified from the Prescription Register and formed the study population (N= 157,709).

4.2.2 Data collection and definition of variables

The Social Insurance Institution (SII) maintains a large, nationwide pharmacy claims database, the Prescription Register. The register collects records of all reimbursed prescription drugs from all community pharmacies in Finland (Furu *et al*. 2010). Records contain the name, ATC code and strength of the dispensed drug, the number of tablets dispensed, prescribing physician and the dispensing date. Over-the counter drugs are not registered in the Prescription Register unless prescribed by a physician. All drugs in Finland are classified based on their ATC-codes, the group code C10AA comprising statins and C10BA02 the fixed combination of simvastatin and ezetimibe which is available on the Finnish market. According to the reimbursement rules, drugs can be reimbursed to a patient for no more than 3 months per purchase. Individuals who stay in institutional care facilities (such as public nursing homes and hospitals) for consecutive 90 days are not eligible for reimbursements, thus, their drug use is not captured by the registers. These individuals can be traced from another SII register.

Data on age, sex, date of institutionalization and date of death were retrieved from the SII. Data on drug purchases were obtained from the Prescription Register and data on pre-existing CVDs from the Finnish Care Register and from the SII Special Reimbursement Register. The Finnish Care Register (“HILMO”, maintained by the National Institute for Health and Welfare) contains data on primary and secondary discharge diagnoses and surgical procedures from all Finnish hospitals, including outpatient visits to specialized care. An individual patient’s data from different sources were identified and linked together by the person’s social security number.

Prescription Register data were collected on the purchases of the following reimbursable drugs: statins C10AA01-C10AA09 (+ simvastatin-ezetimibe combination, C10BA02), antidiabetics (A10), and cardiovascular drugs coprising beta-adrenoceptor

blockers (C07), nitrates and cardiac glycosides (C01), calcium antagonists (C08), angiotensin-converting-enzyme inhibitors (C01), angiotensin II-receptor blockers (C09), antithrombotic drugs (B01), diuretics (C03) and miscellaneous cardiovascular drugs (C02).

Data on pre-existing CVDs (7 years prior to each study year) were based on the International Classification of Diseases (ICD-9 until Dec 31, 1995 and ICD-10 thereafter).We identified the following CVD-related diagnoses and procedures from the Finnish Care Register: CHD, ischemic stroke/TIA, DM, arteriosclerosis universalis (including PAD), aortic aneurysm, hypertension, coronary artery bypass surgery (CABG), percutaneous transluminal coronary angioplasty (PTCA) and vascular surgery of lower extremity arteries or abdominal aorta. In addition, participants with hypertension, DM, FH and CHD were identified from the Special Reimbursement Register.

Each individual's cardiovascular risk level was estimated using the data retrieved from the health registers. As in Study III, the study population was stratified into three risk categories for each study year: *low risk, moderate risk and high risk groups.* Definitions of the risk groups are presented in Table 4.2. In short, if any of the diagnoses or procedures for CVDs, or DM or FH were detected in the registers at some point during the preceding 7 years, the person was classified into the high risk group. In addition, if a person had any registered purchases of antidiabetic drugs during the current or the previous year, he/she was categorized into the high risk groups.

4.2.3 Data analysis and outcomes in Study IV and V

Yearly *prevalence* and *incidence* of statin use were calculated for the total population and separately for men and women. The same calculations were made stratified by age (70-74, 75-79, and ≥ 80 years) and cardiovascular risk group (low, moderate and high risk). *Prevalence* was defined as the number of persons who purchased statins at least once during the specified study year divided by the total number of persons in the study population at the end of the respective year. *Incidence* in the specified study year was then calculated as the number of new users divided by the number of persons in the study population at the end of the year, excluding those who had purchased statins at least once during the previous year. Of note, "new user" in Study IV refers to those individuals, who had at least one statin purchase during the study year but no purchases during the previous calendar year. Age- and sex-standardized prevalence and incidence rates were estimated using the 2008 community-dwelling population as the standard. Age-and sex-adjusted relative changes (RR) in prevalence (with 95% confidence intervals) were estimated with a log-binomial regression model and changes in incidence were calculated with a Poisson regression model with the year 2000 as a reference.

In Study V, the statin initiators of each nine year cohorts were characterized by age, sex, existing CVDs and cardiovascular medication use. In addition, statin type and efficacy at initiation was recorded. Changes in the characteristics during the nine years of follow-up were described. Persistence was measured using the anniversary method. Statin purchases were identified on four index dates at one-year intervals following the statin initiation date. Statin users were dichotomized into users and non-users at annual index dates. The first index date (the first anniversary of statin initiation) was used in the calculation of the one-year persistence and all four index dates were used for the calculation of the four-year persistence. To qualify as a persistent user on an index date, a person had to have a statin purchase recorded within the previous or following three months. Further, a person was considered to have maintained the treatment persistence if he/she was on statin treatment on an index date and all previous index dates. To demonstrate the four-year persistence, we created a tree model in which the initiators were divided into persistent and non-persistent users or were lost to follow-up (referring to death or institutionalization) at yearly index dates. The dynamics in the persistence were illustrated in the tree model by calculating probabilities for each path of the tree.

All persistence analyses were conducted stratified by age (70-74, 75-79, ≥ 80), sex and risk group. One-year persistence was calculated for each year cohort of statin initiators (2000 to 2007), and additional calculations were made stratified by statin initiation dose. The initiators in 2000 and 2004 cohorts were chosen for the four-year persistence calculations, and as there were only slight differences in persistence between the two cohorts they were combined for the tree model analysis.

4.3 Statistical programs

All statistical analyses for the cohort studies were performed with the NCSS 2007 statistical package. SAS version 9.2 was used for data analysis in Substudies IV and V.

4.4 Ethical considerations

The protocols of the TUVA and UTUVA cohort studies were approved by the Ethical Committee of the Hospital District of Southwestern Finland. All participants signed a written consent. Substudies IV and V were approved by the SII and the National Institute of Health and Welfare. Data linkage for both studies was performed by the SII. Ethics committee approval was not necessary for the register studies since the patients were not contacted and only unidentifiable clinical data were available to the researchers.

Table 4.2 Definition of cardiovascular risk groups according to individual data on pre-existing CVDs and drug use collected from national health registers

	LOW RISK	**MODERATE RISK**	**HIGH RISK**
Data source			
Prescription Register (drug purchases during the specific study year and 1 preceding year[a])	no cardiovascular drugs, no antidiabetics	any cardiovascular drug allowed but no antidiabetics	any cardiovascular drug allowed and/or antidiabetics
Special Reimbursement Register (all valid diagnoses)	none of the predefined diagnoses	hypertension	CHD, DM, FH
Finnish Care Register (diagnoses from 7 years prior to the year when subjects entered the study[b])	none of the predefined diagnoses	only hypertension-related diagnoses	CHD, DM, PAD, ischemic stroke/TIA or CABG, PTCA, vascular surgery of abdominal aorta or arteries
Definition	no register markers found	existing diagnosis of hypertension and/or use of cardiovascular drugs	existing diagnosis of CHD, DM, stroke or PAD and/or use of antidiabetics

CVD = cardiovascular disease; CHD = coronary heart disease; PAD = peripheral artery disease; DM = diabetes mellitus; TIA = transient ischaemic attack; CABG = coronary artery by-pass grafting; PTCA = percutaneous transluminal coronary angioplasty

[a] only those drug purchases that were registered 365 days before and 90 days after the statin initiation date were included in Study V

[b] in Study V, statin initiation date (not the study year) was used as the baseline time-point for identifying the CVD diagnoses and surgical procedures from the Finnish Care Register during the preceding 7 years

5 RESULTS

5.1 Association of cholesterol levels with mortality (Study I)

In a cohort of home-dwelling 70-year-olds low levels of total, LDL and HDL cholesterol were associated with a greater risk of death over a follow-up period of 12 years. When stratified by sex, similar associations were found in women but only low LDL-c predicted higher mortality in men. In additional analyses, similar but somewhat weakened associations between the three lipoprotein fractions and mortality were observed in the 15-year and even in the 20 year-follow-up of the same cohort. In further analyses, adjusted for CVD risk factors and cancer, the associations of TC changed toward a U-shaped curve but became non-significant. In the analyses with cardiovascular mortality as outcome, the TC levels in the lowest quartile (< 5.3 mmol/l) predicted the lowest risk compared to the highest quartile (> 6.7 mmol/l). Regarding HDL-c, the subjects in the lowest quartile (< 1.1 mmol/l) had the highest risk of death. In the adjusted models, LDL-c was analyzed separately and no significant associations were detected (Table 5.1).

Table 5.1 Cholesterol levels and survival in the 12-year follow-up. Hazard ratios (HR) with 95% Confidence Intervals (CI) for cardiovascular and all-cause mortality.

		Cardiovascular mortality[a,b], n of deaths = 81		All-cause mortality[a], n of deaths = 167	
Cholesterol, mmol/l		HR	CI 95%	HR	CI 95%
TC	< 5.3	0.48*	0.24-0.97	0.94	0.58-1.50
	5.3-5.9	0.58	0.29-1.15	0.80	0.49-1.30
	6.0-6.7	0.59	0.30-1.14	0.73	0.45-1.18
	> 6.7	1.00	(reference)	1.00	(reference)
HDL-c	< 1.1	2.73*	1.07-6.98	1.09	0.61-1.94
	1.1-1.3	1.91	0.79-4.64	0.83	0.49-1.43
	1.4-1.6	1.96	0.84-4.54	1.06	0.64-1.77
	> 1.6	1.00	(reference)	1.00	(reference)
LDL-c	< 3.5	0.87	0.59-1.29	1.01	0.78-1.30
	2.5-4.0	0.80	0.52-1.22	1.06	0.80-1.40
	4.1-4.6	1.22	0.85-1.77	1.03	0.79-1.34
	> 4.6	1.00	(reference)	1.00	(reference)
Triglycerides	< 1.0	2.06	0.99-4.29	1.40	0.83-2.36
	1.0-1.2	1.05	0.52-2.09	0.88	0.54-1.43
	1.3-1.7	0.71	0.37-1.36	0.74	0.46-1.18
	> 1.7	1.00	(reference)	1.00	(reference)

[a] adjusted for coronary heart disease, stroke, cancer, diabetes mellitus, hypertension, sex, body mass index and smoking

[b] cancer not included in the analysis for cardiovascular mortality

*statistically significant

5.2 Longitudinal changes in cholesterol levels (Study II)

The cholesterol values measured in the TUVA population in 1991 changed through the follow-up examinations in 2001 and 2006. The average TC and LDL-c levels were significantly lower and the HDL-c levels higher in the follow-ups compared to the baseline. Women had significantly higher TC, LDL-c and HDL-c than men at all three measurements (Table 5.2). Among the 221 subjects who participated in all three examinations, HDL-c increased whereas TC and LDL-c declined, in a similar manner in both sexes. The changes observed from the 1991 examination to the 2011 examination among these subjects were a 21% increase in HDL-c (from 1.40 to 1.70 mmol/l), 12% decline in TC (6.19 to 5.43 mmol/l) and 25 % decline in LDL-c (4.20 to 3.15 mmol/l). No significant changes were observed in the triglyceride levels (Table 5.3). In multivariate models, adjustment for sex, CHD, cancer, smoking, alcohol use, serum creatinine level, BMI and physical performance scores did not appreciably influence the results.

Table 5.2 Mean cholesterol levels of all men and women at baseline and at follow-up in 2006

Mean (SD) cholesterol, mmol/l	**BASELINE 1991**		**FOLLOW-UP 2006**		*P*-value*
	MEN (n= 344)	WOMEN (n= 612)	MEN (n= 60)	WOMEN (n= 161)	P^1; P^2
TC	5.59 (1.06)	6.32 (1.12)	4.73 (0.82)	5.69 (0.93)	< 0.001
LDL-c	3.79 (0.93)	4.23 (1.00)	2.70 (0.69)	3.31 (0.82)	< 0.001
HDL-c	1.17 (0.37)	1.46 (0.43)	1.46 (0.47)	1.77 (0.43)	< 0.001
Triglycerides	1.48 (0.88)	1.43 (0.77)	1.25 (0.64)	1.34 (0.56)	P^1 0.158; P^2 0.135

**P*-values for the difference between the sexes at baseline (P^1) and follow-up in 2006 (P^2), significant at level < 0.05, one-way ANOVA

Table 5.3 Mean cholesterol levels of the subjects who participated in each examination and had no lipid-lowering drugs in use. Mean 15-year change in cholesterol levels.

Mean (SD) cholesterol, mmol/l	**BASELINE 1991** (*n*= 221)	**FOLLOW-UP 2001** (*n*= 221)	**FOLLOW-UP 2006** (*n*= 221)	**Mean 15-year change**,mmol/l (SD)	*P*-value* (15-year change)
TC	6.19 (1.02)	5.56 (0.95)	5.43 (1.01)	–0.76 (1.04)	< 0.001
LDL-c	4.20 (0.90)	3.49 (0.80)	3.15 (0.86)	–1.05 (0.94)	< 0.001
HDL-c	1.40 (0.39)	1.46 (0.39)	1.69 (0.48)	+0.30 (0.37)	< 0.001
Triglycerides	1.33 (0.61)	1.32 (0.57)	1.32 (0.60)	–0.01 (0.63)	0.75

**P*-value significant at level < 0.05, repeated measures ANOVA
SD standard deviation

5.3 Cardiovascular risk and the use of statins at the age of 70 – a comparison of two cohorts (Study III)

The prevalence of CHD (25% vs. 11%), PAD (9% vs. 2%) and dyslipidemia (LDL-c ≥ 3mmol/l) (86% vs. 45%) were higher in the 1920-born (TUVA) cohort than the 1940-born (UTUVA) cohort. Similarly, the mean BP levels were higher in the TUVA cohort but hypertension diagnoses more common in the UTUVA cohort. The mean fasting glucose levels were significantly higher in the UTUVA cohort (5.1 vs 6.0 mmol/l). More people in the TUVA cohort were estimated to have a high cardiovascular risk than in the UTUVA cohort (42% vs 29%). The prevalence of a cerebrovascular disease or DM did not differ significantly between the cohorts. Use of preventive medications was much more common in the 1940 cohort. The greatest increase was observed in the use of statins between the cohorts (1% vs. 36%); the use of antidiabetics and antihypertensives was also more common in the UTUVA cohort. (Table 5.4) In that cohort, of the 272 individuals estimated to have high cardiovascular risk, 63% used statins. Only 14% of all statin users in the cohort were estimated to have a low risk.

Table 5.4 Prevalent cardiovascular diseases, risk factors and preventive medication use among 1920 and 1940 birth cohorts

Characteristic, *n* (%)	**1920, TUVA** *n* = 1032	**1940, UTUVA** *n* = 956	*P-value*
Male	370 (36)	392 (41)	< 0.05
Smoking (current)	116 (11)	113 (12)	0.8
BP level, mean mmHg,(sd)	155/85 (21/10)	145/84 (16/9)	< 0.05
BMI kg/m^2, mean (sd)	26.5 (4.0)	27.7 (4.7)	< 0.001
Glucose level, mean, mmol/l (sd)	5.1 (1.2)	6.0 (0.9)	< 0.001
LDL-c level, mean, mmol/l (sd)	4.1 (1.0)	2.9 (0.9)	< 0.001
HDL-c level, mean mmol/l (sd)	1.4 (0.4)	1.7 (0.5)	< 0.001
Dyslipidemia[a]	794 (86)	412 (45)	< 0.001
Hypertension	345 (34)	479 (50)	< 0.001
DM	140 (14)	146 (15)	0.3
CHD	257 (25)	104 (11)	< 0.001
Stroke/TIA	94 (10)	86 (11)	0.7
PAD	93 (9)	18 (2)	< 0.001
Statin use	9 (1)	339 (36)	< 0.001
Antidiabetic use	103 (10)	143 (15)	< 0.001
Antihypertensive use	420 (41)	534 (56)	< 0.001

[a] subjects with LDL-c ≥ 3 mmol/l; *P-value* significant at level <0.05

TUVA = Turun Vanhustutkimus; UTUVA = Uusi Turun Vanhustutkimus; BP = blood pressure; LDL-c = low-density lipoprotein cholesterol; HDL-c = high-density lipoprotein cholesterol; DM = diabetes mellitus; CHD = coronary heart disease; TIA = transient ischemic attack; PAD = peripheral artery disease

5.4 Statin use among the population of older Finns: prevalence, incidence and channeling of use according to cardiovascular risk (Study IV)

Among the total population of community-dwelling Finns aged 70 and older, the largest group both in 2000 and in 2008 was the moderate risk group comprising those persons without clinical CVD but with diagnosed hypertension and/or use of some cardiovascular drugs. The second largest group was the high-risk group, consisting of persons with CVD or DM. Men were more likely to be in the high-risk group than women and the proportion of high-risk men (among all men) increased from 40% in 2000 to 44% in 2008, whereas the respective proportions in women were 33 and 35%.

Statin use among the older population tripled between the years 2000 and 2008. In absolute numbers, statin purchases were registered for 456 857 persons in 2000 and 538 492 persons in 2008, indicating that the age-and sex-standardized prevalence of statin use increased from 12.2% to 38.7% (RR 3.0, 95% CI 3.0-3.1). A similar increase was observed for both sexes (Tables 5.5a and b). The annual incidence of statin use (the number of new users aged ≥ 70) also increased and nearly doubled during the study period. More specifically, the age-sex-standardized incidence increased from 3.7% to 6.8% (RR 1.8, 95% CI 1.8-1.9). Both prevalence and incidence of statin use were most common among high-risk persons (Figure 5.1).

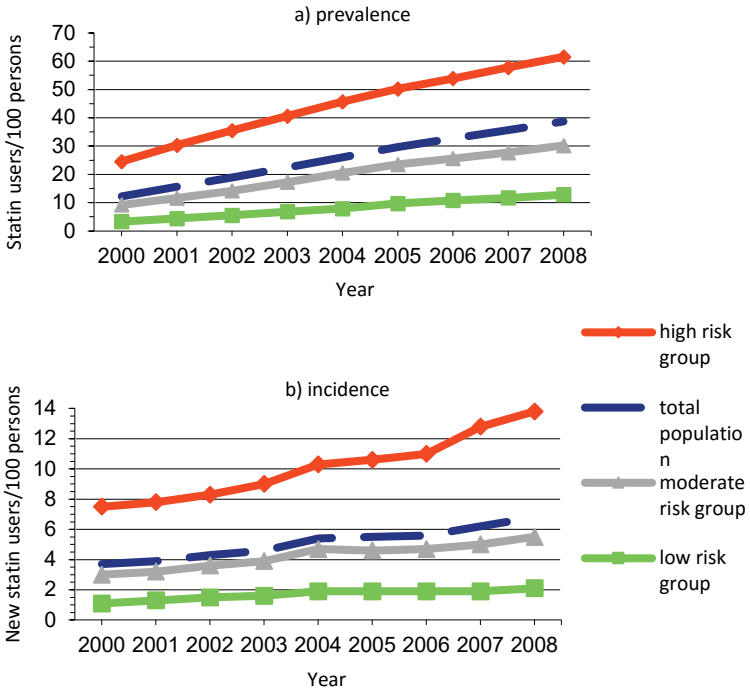

Figure 5.1 Annual prevalence (a) and incidence (b) of statin use among older Finns 2000-2008 by cardiovascular risk group

Table 5.5a Annual prevalence (%) of statin use among older Finnish men 2000-2008, by age and risk group

Men	**2000**	**2004**	**2008**
Age-standardized	11.6	25.0	39.0
(n)	(163 520)	(187 388)	(208 041)
Risk group/Age group			
Total			
70−74 years	16.3	29.6	41.1
(n)	(80 112)	(84 044)	(87 243)
75−79 years	13.2	28.3	42.6
(n)	(49 009)	(59 355)	(66 321)
≥80 years	5.1	17.4	34.0
(n)	(34 399)	(43 989)	(54 477)
Low risk			
70−74 years	2.5	6.7	10.8
(n)	(27 767)	(26 673)	(23 791)
75−79 years	1.8	5.0	10.0
(n)	(13 340)	(15 297)	(13 555)
≥80 years	0.6	2.0	5.8
(n)	(7954)	(10 191)	(8364)
Moderate risk			
70−74 years	9.6	20.6	31.0
(n)	(22 964)	(25 635)	(29 436)
75−79 years	6.5	16.9	28.1
(n)	(14 983)	(18 098)	(22 555)
≥80 years	2.1	8.5	17.9
(n)	(11 288)	(13 865)	(18 760)
High risk			
70−74 years	34.5	56.1	71.0
(n)	(29 381)	(31 736)	(34 016)
75−79 years	25.2	49.9	68.1
(n)	(20 686)	(25 960)	(30 211)
≥80 years	9.6	31.4	53.7
(n)	(15 157)	(19 933)	(27 353)

n= number of persons in the group

Table 5.5b Annual prevalence (%) of statin use among older Finnish women 2000-2008, by age and risk group

Women	**2000**	**2004**	**2008**
Age-standardized	12.6	26.7	38.6
(n)	(293 337)	(315 414)	(330 451)
Risk group/Age group			
All			
70−74 years	18.3	31.9	41.2
(n)	(113 490)	(112 019)	(109 255)
75−79 years	14.0	30.4	42.8
(n)	(92 083)	(96 568)	(99 434)
≥80 years	4.8	17.1	31.2
(n)	(87 764)	(106 827)	(121 762)
Low risk			
70−74 years	5.8	12.8	17.5
(n)	(39 529)	(36 305)	(30 641)
75−79 years	3.3	9.8	16.2
(n)	(23 918)	(23 644)	(19 270)
≥80 years	0.9	3.6	8.8
(n)	(16 191)	(19 680)	(14 824)
Moderate risk			
70−74 years	15.9	30.0	39.0
(n)	(43 661)	(45 864)	(49 373)
75−79 years	10.2	24.8	36.2
(n)	(37 431)	(40 316)	(45 791)
≥80 years	2.9	11.8	22.0
(n)	(36 358)	(43 858)	(55 262)
High risk			
70−74 years	37.8	58.1	69.9
(n)	(30 300)	(29 850)	(29 241)
75−79 years	26.8	52.1	66.5
(n)	(30 734)	(32 608)	(34 373)
≥80 years	8.7	28.7	47.4
(n)	(32 215)	(43 289)	(51 676)

n= the number of persons in the group

The greatest relative increases in both persistence and incidence were observed in those aged ≥ 80 years and in those at low cardiovascular risk, even though the proportion of statin users at low risk remained the same across the years (~7 % of all users). Similar trends were observed in both sexes (Figures 5.2a,b and Tables 5.5a, b).

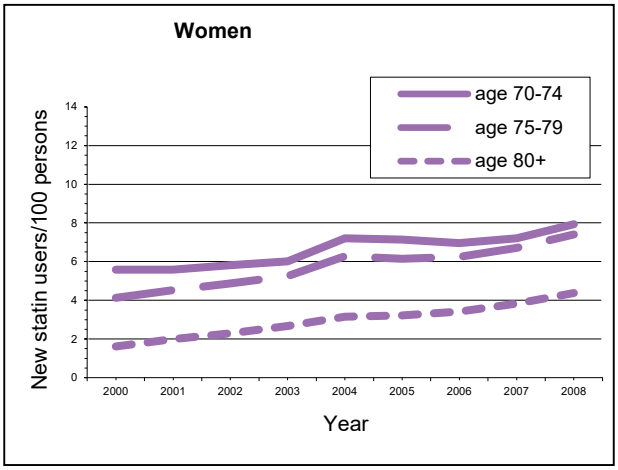

Figure 5.2a Annual incidence of statin use in Finnish women 2000-2008 by age group.

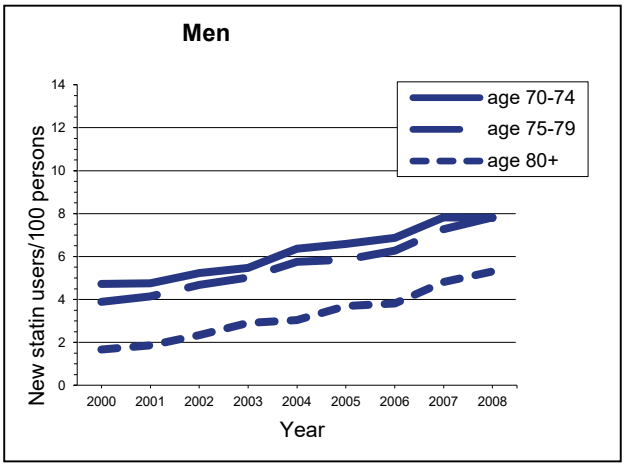

Figure 5.2b Annual incidence of statin use in Finnish men 2000-2008 by age group.

5.5 Cardiovascular risk profiles and persistence of statin use among new statin users (Study V)

The same cardiovascular risk classification was used among the yearly cohorts of statin initiators.The number of statin initiators increased from 15,082 to 19,728 from 2000 to 2008. Among them, the proportion of men increased from 35.6% to 41.5%. The mean age at statin initiation increased from 75.8 to 77.4 years and the proportion of initiators aged 80 and older doubled (from 12.9% to 25.8%) (Figure 5.3).

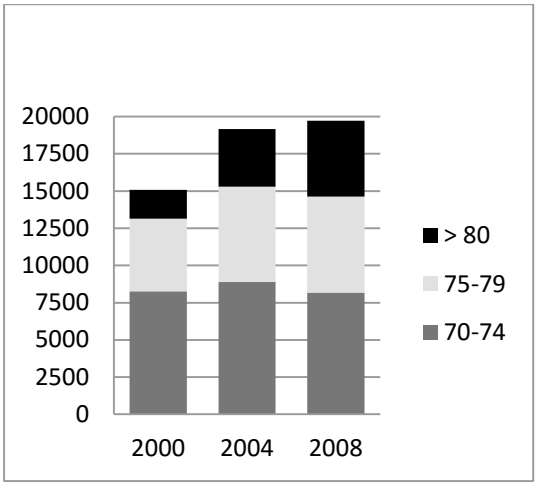

Figure 5.3 The number of statin initiators stratified by age group

The prevalence of CHD at statin initiation decreased from 45.5% to 28.1%. In 2000, one-third of the initiators were estimated to have a moderate cardiovascular risk and two-thirds high risk, whereas in 2008, the respective proportions were 39.2% and 51.2%. Men were more likely to belong to the high risk group each year. The number of low-risk initiators remained low (≤ 10%) across the years (Figure 5.4). The most common statin at initiation was simvastatin (42.3% in 2000 and 96.3% in 2008). The most common statin dose was 10mg until 2002 and 20mg thereafter.

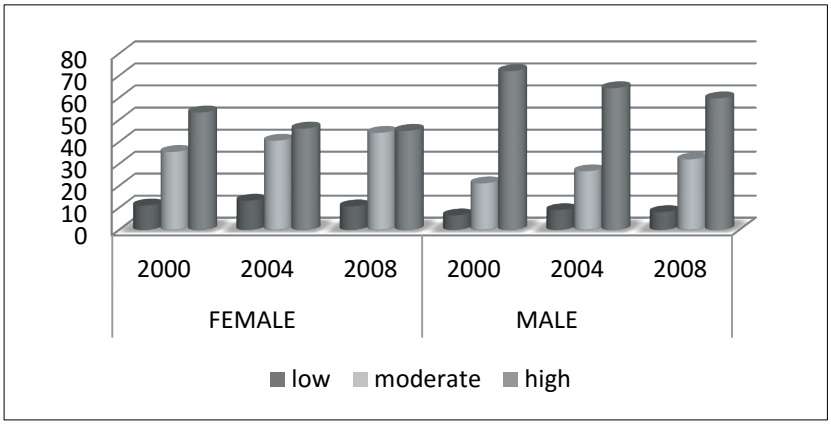

Figure 5.4.
Statin initiators (%) stratified by sex and cardiovascular risk group: low, moderate and high risk

One year after statin initiation, the persistence was fairly good across all year cohorts, varying from 76.9% to 80.5%. After the exclusion of the lost individuals, the proportion of those remaining persistent for four years was 62.8% (a weighted average of the combined initiator cohorts of 2000 and 2004). The declining trend in persistence was similar across all cardiovascular risk groups, only slightly pronounced in the low risk group. The observed persistence trends did not change when stratified by age group or sex. The dynamics of statin persistence in the four-year follow-up were illustrated in a tree model (Figure 5.5), in which the probabilities for the three main paths were calculated: the individual remains a persistent user and survives (51.6%); the individual discontinues statin use during the first year without restarting the use by the end of the follow-up (9.1%); the individual persists with statin use for the first year and discontinues it after that without restarting during the follow-up period (3.5%). According to the tree model, about two-thirds of the initiators remained persistent for two years and almost 60% for four years. At year four, 61% of all initiators (21,114 people) were still using statins, most of them as continuous users and some of them as intermittent users who once had discontinued but later restarted their use.

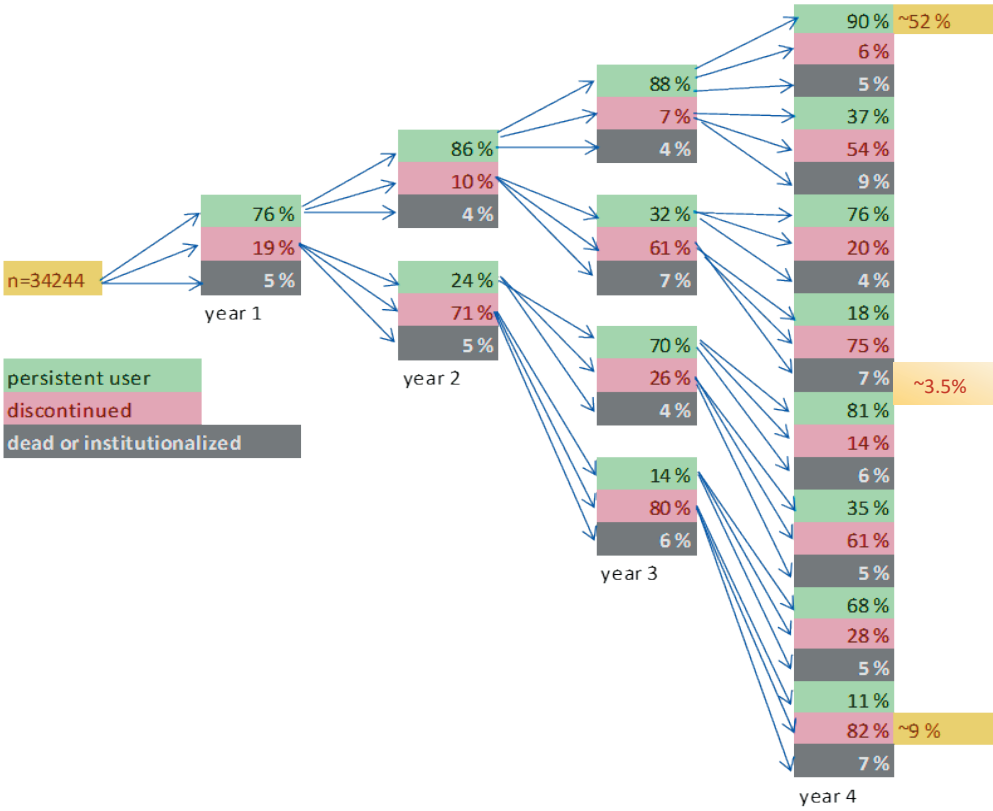

Figure 5.5 Tree model illustrating dynamics in persistence of statin use (combined year cohorts of statin initiators from 2000 and 2004)

6 DISCUSSION

Low TC, LDL-c and HDL-c were associated with higher all-cause mortality in a long-term follow-up of home-dwelling 70-year-olds. With regard to cardiovascular mortality, low levels of TC seemed to be protective whereas low levels of HDL-c predicted an increased risk of cardiovascular death. In the same cohort, the cholesterol levels of those elderly who stayed in the follow-up and were still home-dwelling at the age of 85 seemed to improve with advancing age. Further, compared to the TUVA cohort of 1991, the UTUVA cohort of 2011 had fewer CVDs, and their risk factors were better controlled. This was reflected in a higher use of preventive medications, such as statins and antihypertensives. Among the total Finnish population aged 70 and older, statin use increased significantly during 2000–2008, also among the oldest (80+) age groups. Most statin users had a high cardiovascular event risk indicating that the treatment was well directed towards those who are likely to benefit the most. Approximately two-thirds of the new statin users were still persisting with the use four years after the initiation. The decision on whether to continue or discontinue statin use that was made during the first year seemed to predict later use.

6.1 Changes in cholesterol levels with aging and association of cholesterol with cardiovascular disease and mortality

During this long-term follow-up of a cohort of 70-year-olds, an inverse association was observed between the baseline serum TC, LDL-c and HDL-c levels and all-cause mortality, corresponding to the results from previous prospective studies (Weverling-Rijnsburger *et al.* 1997, Schatz *et al.* 2001, Tuikkala *et al*. 2010). However, after adjustment for several confounders, such as existing CVDs, cardiovascular risk factors or cancer, the observed mortality associations changed and suggested a U-shaped association between the TC levels and mortality, as reported by a few other cohort studies (Corti *et al*. 1997, Curb *et al*. 2004). With regard to the associations of cholesterol and cardiovascular mortality, these results were similar to those observed in younger adult populations (Lewington *et al.* 2007), that is, a lower TC (< 5.3 mmol/l) predicted a lower risk of death. Furthermore, as reported by others (Corti *et al.* 1995, Weverling-Rijnsburger *et al.* 2003, Packard *et al*. 2005), the significance of HDL-c as a risk predictor in the elderly was confirmed by this study. Having a HDL-c level in the lowest quartile (< 1.1 mmol/l) was associated with a 2.7 times higher cardiovascular death risk compared to a HDL-c level of > 1.6 mmol/l in a 12-year follow-up period. In contrast to this, LDL-c seemed to have poor predictive value when measured at the age of 70, as no association at all was found between LDL-c and cardiovascular or total mortality in the adjusted analyses.

The observed inverse association of TC to mortality, in other words “the higher the better” is commonly found in cohort studies consisting of older persons and has been

called the cholesterol paradox of old age (Hazzard and Ettinger 1995). It has been suggested that those individuals who survive until an older age represent a selected population who might be more resistant to atherogenetic effects of cholesterol than those who suffer from atherosclerotic diseases and die or become institutionalized at younger ages (Morley 2011). However, a similar phenomenon, a reversed epidemiology, has been shown to apply to other traditional CVD risk factors when assessed in older populations (Vischer *et al.* 2009). Higher blood pressure rather than low has seemed to be a protective factor against mortality (Vischer *et al*. 2009). Similarly, a high BMI compared to "normal" or low weight has correlated with better survival (Diehr *et al*. 2008, Nilsson *et al*. 2011). The concept of reversed epidemiology has been explained by the heterogenity of older persons and an increased incidence of non-CVD caused deaths that dilute the associations between traditional risk factors and CVD in cohort studies (Vishcer *et al*. 2009, Koller *et al.* 2012, Strandberg *et al.* 2014). Furthermore, a low plasma cholesterol level, low weight and low BP have been linked to frailty (Singh *et al.* 2014). Thus, they could indicate chronic inflammation or subclinical disease, which later manifests as a clinical disease, such as dementia, CHD or chronic heart failure.

Moreover, cholesterol metabolism undergoes changes during the aging process, affecting the serum levels measured at a specific age and thereby influencing their value as a risk predictor (Tilvis *et al.* 2011). In this study, the cholesterol levels of 70-year-old men and women were observed to improve during a 15-year follow-up period, even in the absence of (statin) treatment. HDL-c increased significantly throughout the follow-up period, in contrast to most previous studies (Wilson *et al*. 1994, Weijenberg *et al*. 1996, Ferrara *et al*. 1997) with the exception of the Honolulu Heart Study cohort, where a similar but smaller increase was observed in the HDL-values during a 10-year follow-up of elderly men (Abbot *et al*. 1998). Similar TC and LDL-c declines have been reported previously, mainly from cohorts consisting of elderly men (Abbot *et al*. 1998, Wilson *et al*. 1994, Weijenberg *et al*. 1996). It is noteworthy, that these favourable lipid changes were observed only in the 221 home-dwelling older persons, predominantly women, who survived and stayed in the study for 15 years. Whether there were similar changes in the lipid profiles of those elderly, who died, or were institutionalized during the follow-up, remains unanswered by this study. It is, however, unlikely that frailty or subclinical disease was the reason behind the observed declines in the TC/LDL-c levels of these persons considering the simultaneous clear rise in their HDL-c levels.

6.2 Trends in statin use from 2000–2008: prevalence, incidence and persistence of use

During the observation period of nine years, there was an almost linear increase in the prevalence of statin use among the Finnish population aged 70 and older, corresponding to the results of an earlier Finnish register study from 1995 to 2005 (Ruokoniemi *et al*. 2008). The number of prevalent users tripled during the 9-year period, and by 2008 almost 40% of the older population used statins. Another Finnish register study covering the same time period, reported an increasing trend toward lower level indications in statin prescribing among total adult population (Rikala *et al*. 2013). Among the older population, however, the proportion of low-risk statin users stayed low and stable across the years (at about 7%) and most statin users were estimated to have a high cardiovascular event risk. The increases in prevalence and incidence were similar across all the cardiovascular risk groups. Although relatively high increases were seen among the low-risk individuals, the increase was most prominent among the high-risk persons, 25% using statins in 2000 and almost two-thirds in 2008. Interestingly, a slight sex difference was seen in the channeling of statin use, previously observed by another study as well (Wallach-Kildemoes *et al.* 2011).There were more women than men among the low-risk users indicating that women are already prescribed statins at a lower risk level, presumably as older women are more active regarding health-seeking behavior than men.

In several earlier studies, underuse or underprescribing of statins has been observed among older high-risk persons (Hamilton-Craig *et al*. 2015). The results of this study indicate, that at least in Finland, the suspected ageism might have disappeared, as both the prevalence and incidence of statin use increased strongly also among the oldest 80+ age group. In addition, among all new statin users the share of persons aged ≥ 80 increased considerably over the years (from 13% to 26%). One explanation for this channeling is that many of the "young-olds" were already prevalent statin users and therefore not eligible as new users in Study V. The majority of the yearly statin initiators were estimated to have at least a moderate risk of CVD events and the share of initiators at low risk remained below 10% across the observation period.

As presented in the reviews by Petersen *et al*. (2010) and Strandberg *et al*. (2014), only few RCTs reporting on statin benefits have included over 80-year-olds and none of these was specifically designed for individuals aged ≥80 at baseline. Thus, it may be debated whether there has been some overuse of statins among the oldest age groups. Without any conclusive evidence from RCTs, physicians have been extrapolating the results and treatment recommendations derived from younger populations to the oldest age groups and may have even overestimated their CVD risks. However, it would not seem ethical to leave the oldest persons without effective treatment just because trial data are lacking. The most recent review updated the results of statin RCTs and observational studies, focusing on persons 80 and older, and emphasized the importance of individual treatment decisions for the oldest elderly (Strandberg *et al.*

2014). Physicians should consider the comprehensive health status and functionality of the older patient and respect his/her own wishes before initiating preventive drug treatment.

Statins are preventive drugs that need to be taken regularly and long-term in order to benefit from them the most. Studies on statin adherence have previously reported relatively poor persistence rates for older persons (Jackevicius *et al*. 2002, Simons *et al*. 2011). In an Australian study of persons aged 65-74, over 40% had discontinued statin use by 6 months (Simons *et al*. 2011). Only a few studies have assessed the long-term adherence or persistence of the elderly (Benner *et al*. 2002, Helin-Salmivaara *et al*. 2008, Simons *et al.* 2011, Warren *et al*. 2013), and some have observed that older individuals persist better with the prescribed drug treatment than younger ones (Mantel-Teeuwisse *et al.* 2004, Warren *et al.* 2013). In most studies, primary prevention or low-risk indication has been associated with worse persistence (Jackevicius *et. al* 2002, Mann *et al.* 2010, Warren *et al*. 2013). In the present study, persistence dropped the most during the first year of treatment, corresponding to previous studies. During the four-year follow-up, persistence gradually declined in a similar manner across all cardiovascular risk groups, yet the steepest decline was seen in the low risk group. Up to two-thirds of the survivors followed-up for four years persisted with the statin treatment. In addition, those who persisted with the use over the first year were the ones most likely to persist through the following years as well.

Poor adherence or early discontinuation of a prescribed statin treatment potentially has serious clinical consequences, an increased risk of CVD events and even mortality (Liberapoulos *et al*. 2008). The concept of sub-optimal adherence to medications is poorly recognized by clinicians (Osterberg and Blaschke 2005) and applies to other preventive cardiovascular medications as well, such as beta-blockers or ACE inhibitors. A large meta-analysis reviewed studies that reported associations of cardiovascular medication adherence (including statins) to CVD events (Chowdhury *et al*. 2013). The authors estimated that a total of 9% of all the CVD events in Europe could be attributed to poor adherence to cardiovascular medications alone. Thus, physicians should be made more aware of this issue and focus on how to encourage their patients to persist with the prescribed medication, especially over the important first year of use. When starting a new drug treatment, physicians should carefully explain the benefits and possible unwanted effects of the drug to the patient and his/her care-givers. Regular controls should be arranged in which the medication adherence is openly discussed together with the patient and/or the care-giver (Tarn *et al*. 2012). Patients' complaints on the possible adverse effects, such as the muscle symptoms associated with statin use should be taken seriously. In the event that one statin seems to cause problems, a trial with another preparation should be made by initiating at a low dose.

6.3 Changes in cardiovascular risk factors and preventive drug use between 1991 and 2011

The 70-year-olds in 2011 were healthier in terms of CVD morbidity than the 70-year-olds 20 years earlier. In particular, the prevalence of CHD and PAD was higher in the earlier cohort, which may partly be due to differences in the diagnostic methods between the two cohorts. The overall cardiovascular risk profiles in the 1940 cohort were better, with lower BP levels and more favourable lipid profiles, including lower TC, LDL-c and triglycerides and higher HDL-c levels, which corresponds to the improvements reported in the risk factors of adult Finnish population during past decades (Vartiainen *et al.* 2010). The increased use of preventive drugs, such as statins and antihypertensives is likely to have influenced the improved risk profile and smaller prevalence of CHD in the later cohort. The proportion of statin users increased from 1% to 36% between the cohorts, reflecting the growth in statin use among the total Finnish population. Further, the channeling of statin use inside the 1940 cohort matches the results derived from the register studies even though examination of the cohort took place three years after the last year included in the register study. Following the national guidelines, statins were most commonly used by persons estimated to have a high cardiovascular event risk. However, one-third of the high-risk individuals did not use statins at all, for reasons which, unfortunately were not analyzed by this study.

Stroke prevalence did not differ significantly between the cohorts, contradicting the results of an earlier study (Zhi *et al*. 2013). However, this could be explained by the age of our populations, as stroke incidence peaks at a somewhat higher age (75+) (Heart disease and stroke statistics, update 2014). Interestingly, the prevalence of the DM diagnoses was almost equal in the two cohorts. However, the mean glucose levels and antidiabetic drug use were clearly higher in the 1940 cohort, indicating that DM actually was more common in the later cohort. Type 2 DM risk is strongly linked to obesity (Grundy *et al*. 2005), and corresponding to this, the mean BMI level of the 1940 cohort was indeed slightly higher than that of the 1920 cohort (26.5 vs. 27.7 kg/m^2). These observations are concerning and reflect the increasing incidence of type 2 DM in Western countries, especially among middle-aged or older adults (Grundy *et al.* 2005, Vartiainen *et al.* 2010, Zhi *et al*. 2013).

Overall, the results concur with the global and nationwide trends of the declining incidence of CVD events (European Heart Network: European statistics 2012, Heart disease and stroke statistics update 2014, NIHW statistical database 2014, Vartiainen *et al.* 2010).There were significant improvements observed in the later cohort in two important CVD risk factors, BP and cholesterol levels, leading to the conclusion that the national health promotion interventions successfully implemented in the Finnish population since the North-Carelia project are reflected in the improvements of the CVD risk profiles of today's elderly population. Unfortunately, this trend may be changing for the worse in the near future, as increasing incidence of metabolic

syndrome and type 2 DM among (older) adults is predicted to be reflected in higher rates of CVD in the next decades (Grundy *et al.* 2005, Crimmins 2010).

6.4 Strengths and limitations

The birth cohort design in Studies I, II, III enhances the homogenity and representativeness of the populations. Participation rates were good and comparable in both cohorts. As only the home-dwelling elderly were included in all the studies, the results do not apply to the more frail older persons (living in nursing homes). Limitations in comparison of the two cohorts are the unavoidable differences in the diagnostics of CVDs in the Finnish population around the time of the first study in 1991 and the second study in 2011. Even though the study physician in 2011 used the same criteria in examining the participants and confirming the diagnoses as were used in the earlier cohort, most of the previous diagnoses of the participants were based on their medical records and in some cases more strict diagnostic criteria were applied in 2011 than 20 years earlier. For example, the hypertension diagnosis was made based on lower BP targets in 2011 than 20 years earlier, which would explain why the prevalence of hypertension diagnosis was lower even though the mean BP levels were higher in the earlier cohort. Similarly, the diagnosis of PAD was not always confirmed by the ankle-brachial index or an examination by a specialist vascular surgeon in the 1991 examined cohort.

The two register studies were based on data from comprehensive health registers capturing the entire Finnish population aged 70 and older. Hospital information on CVD diagnoses was traced over several years prior to and during each study year. The Prescription Register covered up to 95-100% of statin purchases of the study population. However, the register data did not include information on cholesterol levels or lifestyle factors such as smoking or family history; therefore, the risk classification method used in the two studies has its limitations. Yet, considering the older age of the population and the lack of predictive value of the cholesterol values at that age, classification of the majority of the high-risk persons was likely done correctly. In contrast, it could be argued that some of the subjects classified to low-risk group merely on the basis of not having cardiovascular drug use or valid CVD diagnoses should actually belong to at least the moderate risk group based on their higher age and, thus, higher probability of subclinical atherosclerosis.

In Study V the long gap (maximum of 365 days) which was allowed between two consecutive statin purchases may have led to overestimation of persistence. In addition, the methods used did not measure adherence. However, adherence and persistence have also been defined as two sides of the same issue, and in studies which have separately assessed both adherence and persistence, individuals who have been defined as good adherers (PDC ≥ 80%), have also been those with better persistence (Van Wijk *et al*. 2006, Helin-Salmivaara *et al*. 2008). Furthermore, statin use is shown to be dynamic, and temporary interruptions occur during long-term treatment (Korhonen *et*

al. 2009*)*. Finally, even though the statin purchases of the population could be tracked from the Prescription Register, there is no certainty that all purchased statins were actually taken by the individuals.

6.5 Benefits of screening and treatment of dyslipidemia in older age

The issue of screening and treatment of dyslipidemia in the elderly remains controversial. At the population level, most cardiovascular events occur in individuals without previously diagnosed CVD (Rose 1985, Hingorani *et al.* 2009); thus, more emphasis should be placed on primary prevention. However, evidence from recent genetic studies has indicated that the treatment of dyslipidemia at an older age may be too late (Ference *et al*. 2012). Maintaining low levels of LDL-c throughout life may prevent or substantially delay the development of atherosclerosis. Therefore, a healthy lifestyle and drug treatment aiming at the prevention of atherosclerosis and CVD should start as early as possible, in adolescence at the latest in order to prevent premature death or disabilities in old age (Ference *et al*. 2012). Based on this, it has been discussed whether statin treatment initiated at an older age has any long-term beneficial effects at all (Desai *et al*. 2011, Odden *et al*. 2015) (Figure 6.1). Then again, the pleiotropic effects of statins in stabilizing the atheroschlerotic plaques and preventing them from rupturing (thereby reducing ischemic events) might be beneficial at any age.

In secondary prevention or in the high-risk elderly, the existing evidence supports the use of statins in CVD prevention at least up to the age of 80, based on RCTs. Observational data on statin benefits have included even older age groups. There is no evidence to show that statins would cease being beneficial after the person reaches a certain age. Thus, physicians should consider the comprehensive health status and functionality of individual older patients when deciding on starting or discontinuing treatment for dyslipidemia. The older and the more frail the patient gets, the more complex is the decision-making and the more individualized clinical judgement is needed. Independently-managing older persons may be screened for dyslipidemia and treated based on the total CVD risk estimation similarly to younger ones. In frail older persons, the adverse effects may outweigh the beneficial effects. Finally, when the estimated life expectancy is only a few years, statin treatment is probably no longer worthwhile.

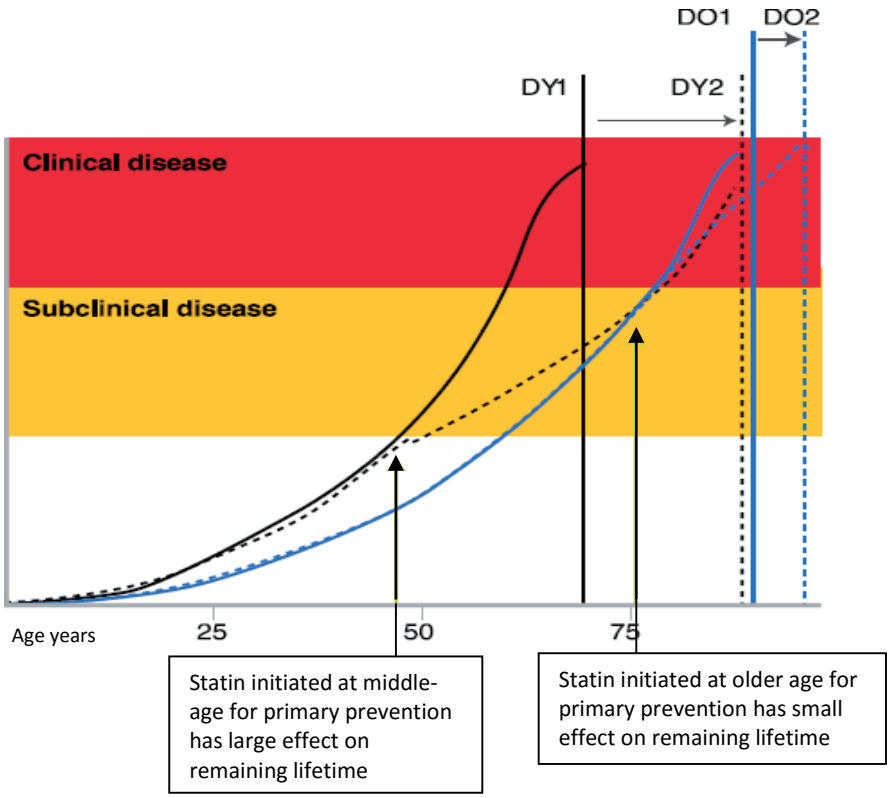

Figure 6.1. Effect of age on statin initiation based on cardiovascular disease trajectory and age (Modified from Desai *et al.* 2012, with permission to reproduce from *Springer*)
DY1 = death young, no statin; DY2 = death when statin initiated at middle age; DO1 = death old, no statin; DO2 = death, when statin initiated at older age

7 CONCLUSIONS AND IMPLICATIONS

Low plasma cholesterol levels, especially low HDL-c, seem to predict a poorer prognosis and higher risk of mortality in older populations. Furthermore, HDL-c is a better predictor of a CVD risk than LDL-c in older persons. The associations of cholesterol levels with CVD and mortality are not straightforward in older populations, as the heterogenity among older persons and competing causes of death confound the associations observed in cohort studies. In addition, the cholesterol values of older persons undergo changes with advancing age as part of the physiological aging process.

The 70-year-olds in 2011 had less CVD morbidity and had cardiovascular risk factors better controlled than their counterparts 20 years earlier, owing at least in part to their higher use of preventive medications, such as statins and antihypertensives. Increases in fasting glucose levels and use of antidiabetic drugs indicate a higher prevalence of DM among the later-born cohort of 70-year-olds, which may reflect unfavorable lifestyle and dietary changes of the last decades.

During the 2000s, statin use increased considerably among the Finnish older population, also among the oldest 80+ age groups. Statin use seemed to be guideline-based, as it was directed towards the high-risk persons, even though there is a lack of data on the benefits of statins in the oldest age groups. Two-thirds of the older persons who initiated statin use were (still) using it four years later. Most discontinuations were made during the first year of use.

Clinical implications

With increasing life expectancy, the number of older people at risk for CVD is rapidly growing. Healthy 70-year-olds may have 20 or more “good” life-years ahead. Today, vascular procedures such as coronary stenting or aortic surgery are routinely performed for 80 or even 90-year-olds. Prevention of the disease outcome is always cheaper than treating the complications. In old age, quality of life is often valued more than the number of years ahead; however, quality of life is definitely worse after having had a stroke than before. Hence, preventive and effective drug treatments such as statins should be offered to older persons, irrespective of age but based on individual benefit-risk assessment that takes into consideration each individual’s overall health and functional capacity.

Although the cholesterol values measured at an older age have less predictive value than at a younger age, screening of dyslipidemia at the age of 70 or older can be recommended as a part of the total cardiovascular risk estimation. However, treatment decisions should be guided by the clinical disease or risk factor burden rather than by

single cholesterol values. Lifestyle modifications should always be considered, but their role in CVD prevention probably becomes less significant in older age.

Physicians should pay more attention to adherence issues when prescribing preventive medications as premature discontinuation of use may have serious clinical consequences. Regular controls should be arranged to address treatment adherence, especially during the first year of use. Statins should be initiated at a low or moderate dose and dose titration be done with caution to avoid adverse effects, such as the muscle symptoms.

To conclude, there are still many open questions concerning the significance of dyslipidemia and the benefits of statin treatment in old age. We need long-term observational studies and RCTs designed for people aged 70 and older and especially those aged 80 and older, to address these issues. Future studies should also include frail older persons and those who live in nursing homes in order to improve the generalizability of the results among the heterogeneous older population that clinicians are dealing with in everyday life.

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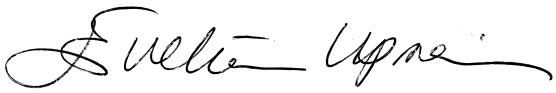

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