Thesis for the degree of Doctor Scientarium

A pharmacoepidemiological study of lipid-lowering drugs in Norway

Sales of lipid-lowering drugs in Norway 1994-2005

Ingeborg Hartz

2006

Department of Pharmacoepidemiology and Pharmacy Practice
Institute of Pharmacy, Faculty of Medicine
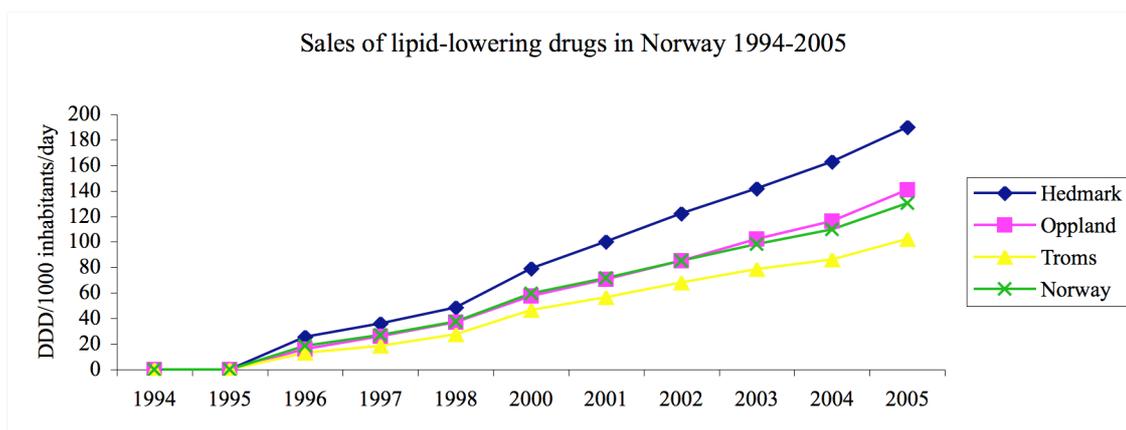**University of Tromsø, Norway**

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Contents

inclusion of me has been a premise to complete this thesis. An absolute premise. Thank you!

During the years in Elverum I have repeatedly received invitations from research colleges at the Department of Pharmacoepidemiolgy, National Institute of Public Health, in Oslo. Including me and my project into this professional as well as social working environment has been an enormous inspiration during the last years. A special thank to you, Svetlana, for always having time, and for your continuous thoughtfulness in pharmacoepidemiological and personal matters!

And last, I would like to thank my family and friends, including my parents Inger and Tore, my long way back friend and college Pia, and my special friend Bjørn in particular. The time that Tore (jr) and I have shared with you all, have represented a highly appreciated contrast to my world of p-values, SAS-syntax and lipid-lowering drugs.

List of papers

The thesis is based on the following papers:

I   Hartz I, Eggen AE, Grimsgaard S, Skjold F, Njølstad I. Whom are we treating with lipid-lowering drugs? Are we following the guidelines? Evidence from a population-based study – the Tromsø Study 2001. *Eur J Clin Pharmacol* 2004;**60**;643–9.

II   Hartz I, Njølstad I, Eggen AE. Does implementation of the European guidelines based on the SCORE model double the number of Norwegian adults who need cardiovascular drugs for primary prevention? The Tromsø Study 2001. *Eur Heart J* 2005;**26**:2673–80.

III   Hartz I, Skurtveit S, Furu K, Njølstad I, Eggen AE. Why do sales of lipid-lowering drugs vary between counties in Norway? Evidence from the OPPHED Health Study 2000-2001. *Scand J Prim Health Care* 2006;**25**:115–21.

IV   Hartz I, Sakshaug S, Furu K, Engeland A, Eggen AE, Njølstad I, Skurtveit S. Aspects of statin prescribing in Norwegian counties with high, average and low statin consumption - an individualised prescription database study. Submitted.

The papers will be referred to by their Roman numerals in the text

Abbreviations

4S	=	Scandinavian Simvastatin Survival Study
A to Z	=	Aggrastat to Zocor
AFCAPS/TexCaps	=	Air Force/Texas Coronary Atherosclerosis Prevention Study
ALT	=	alanine aminotransferase
ASCOT-LLA	=	Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm
AST	=	aspartate aminotransferase
ATC	=	Anatomical Therapeutic Chemical classification system
CARDS	=	Collaborative Atorvastatin Diabetes Study
CARE	=	Cholesterol and Recurrent Events Trial
CHD	=	Coronary heart disease
CPR	=	Central Population Registry
CVD	=	cardiovascular disease
CYP	=	cytochrome P450
DDD	=	defined daily dose
EUROASPIRE	=	European Action on Secondary Prevention by Intervention to Reduce Events
GP	=	general practitioner
HDL-C	=	high-density lipoprotein-cholesterol
HMG-CoA	=	3-hydroxy-3-methylglutaryl coenzyme A
HPS	=	Heart Protection Study
IDEAL	=	Incremental Decrease in Events through Aggressive Lipid Lowering
LDL-C	=	low-density lipoprotein-cholesterol
LIPID	=	Long-Term Intervention with Pravastatin in Ischaemic Disease
LLD	=	lipid-lowering drug
MI	=	myocardial infarction
NNT	=	number needed to treat
NOK	=	Norwegian kroner

NorPD	=	Norwegian Prescription Database
OPPHED	=	health survey in the Norwegian counties Oppland and Hedmark
PROSPER	=	PROspective Study of Pravastatin in the Elderly at Risk
PROVE-IT	=	Pravastatin or Atorvastatin Evaluation and Infection Therapy
SCORE	=	Systematic Coronary Risk Evaluation
TC	=	total cholesterol
TG	=	triglycerides
TNT	=	Treating to New Targets
WOSCOPS	=	West of Scotland Coronary Prevention Study

1. Introduction

1.1 Trends in the consumption of lipid-lowering drugs in Norway

Early clinical trials on lipid-lowering drugs (LLDs) used bile acid sequestrants

(resins) or fibric acid derivatives (fibrates), and demonstrated statistically significant

relative reductions in cardiovascular morbidity.[1,2] However, only modest reductions of

total cholesterol (TC) levels were achieved, and the production of unpleasant adverse

effects was significant. Concerns about the increase in non-cardiac mortality, for

fibrates in particular, together with no effect on total mortality, limited the use of

these drugs.[2,3] In the 1990s the advent of agents called statins was introduced to the

market, which offered a new alternative to modify lipids safely and effectively with

drug therapy. Hence, the 'statin era' in Norway began in 1994, with publication of the

mortality benefits of reductions in serum cholesterol, demonstrated by the

Scandinavian Simvastatin Survival Study (4S).[4] As a result, sales of LLDs have

increased markedly in Norway since 1994, and show significant county differences[5]

(Figure 1). Sales in Norway are high compared with those in other Scandinavian and

European countries[5-8] (Figure 2). The statins made up 99.5% of the sales of all LLDs

in 2005, and the overall increase in LLD sales is due to an increasing consumption of

statins.[5]

Figure 1. Sales of lipid-lowering drugs (ATC-group C10A) in defined daily doses (DDDs) per 1000 inhabitants per day in three Norwegian counties and mean for Norway, 1994–2005.

Figure 2. Sales of lipid-lowering drugs (ATC-group C10A) in defined daily doses (DDDs) per 1000 inhabitants per day in Scandinavia, 1995–2005.

1.2 Statins: pharmacological and clinical aspects

Currently, five statin substances are licensed for use in Norway: lovastatin,

simvastatin, pravastatin, fluvastatin and atorvastatin.

Table 1. Characteristics of statins licensed for use in Norway[1]

	Atorvastatin	Simvastatin	Pravastatin	Fluvastatin	Lovastatin
Absorption (%)	30	60-85	35	98	31
Bioavailibility (%)	12	< 5	17	10-35	< 5
Metabolism	CYP3A4	CYP3A4	Sulfation	CYP2C9	CYP3A4
Prodrug	No	Yes	No	No	Yes
Half-life (hours)	13-30	1-3	2-3	0.5-3	2-4
Licenced max dose (mg)	80	80	40	80	80
TC reduction (%)	42	37	27	27	32
LDL-C reduction (%)	55	48	34	34	41
HDL-C increase (%)	4-8	4-8	4-8	4-8	4-8
TG reduction (%)	25-35	20-30	10-20	10-20	15-25
Equipotent dose (27% TC reduction)	10	20	40	80	40

[1] From [9-11]

1.2.1 Lipid-lowering action

The enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase

converts HMG-CoA to mevalonic acid, which is the rate-limiting step in cholesterol

biosynthesis in the liver and other tissues. Statins are structurally similar to HMG-

CoA, and lower cholesterol biosynthesis by a competitive inhibition of HMG-CoA

reductase. [10,11] Furthermore, the reduction in hepatocyte cholesterol concentration

triggers increased expression of low-density lipoprotein-cholesterol (LDL-C)

receptors in hepatocytes, leading to increased clearance of LDL-C from the

circulation. [10,11] This mechanism is the most widely accepted mechanism for an

explanation of the clinical benefits of statins observed in multiple randomized clinical trials.[12]

The statins exhibit variable dose-related efficacy in reducing serum lipids (reducing LDL-C, total cholesterol (TC) and triglycerides (TG), and increasing high-density lipoprotein cholesterol (HDL-C)),[13,14] which may be attributed to differences in their pharmacodynamic (enzyme binding) as well as their pharmacokinetic properties. [10,11] When compared at milligram-equivalent doses, atorvastatin produces the greatest reductions in TC and LDL- C, followed by simvastatin, pravastatin, lovastatin and fluvastatin.[13,15]

Although there have been a number of trials comparing the statins using cholesterol reduction as a surrogate end-point, it is still uncertain to what extent these results can be extrapolated to clinically relevant outcomes. However, a recent study suggests that similar degrees of lipid reduction with pravastatin, simvastatin and atorvastatin may be translated into similar benefits for cardiovascular end-points.[16]

1.2.2 Non-lipid actions

Inhibition of mevalonate synthesis reduces cholesterol production, but it also inhibits production of a diverse group of proteins that have an important role to play in cellular function. The non-lipid effects of statins can be divided into clinically beneficial and clinically detrimental ones. The beneficial non-lipid, or so-called pleiotropic, effects of statins include improvement of endothelial function, stabilization of atherosclerotic plaques, prevention of thrombus formation, and an anti-inflammatory and immunomodulatory effect.[17] The details of the mechanisms involved in these pleiotropic effects, and the potential differences among the variable statins, are still unclear.[18] The main question is to what extent the pleiotropic effects of statins account for the improvement in cardiovascular outcomes beyond that

expected for lipid lowering alone. A recent meta-analysis concluded, however, that the pleiotropic effects may be small compared with the effect of lipid lowering on cardiovascular risk reduction.[12]

Apart from pleiotropic effects, the inhibition of the mevalonate pathway is considered to be the mechanism related to the clinically detrimental effects of statins, including muscular and hepatic effects. The most serious adverse event after statin therapy affects striatal muscles, ranging from myalgia (muscle ache or weakness, with no rise in creatine kinase) to harmful myopathy and potentially lethal rhabdomyolysis (rise in creatine kinase to 10 times the upper limit of normal), and has an association with all the available statins. The myotoxic effect of the statins seems to be dose dependent; about 5–10% may develop raised muscle enzyme levels, but the incidence of myopathy is low at 1 per 10 000 person-years, and even lower for rhabdomyolysis.[19,20] The risk of developing a myotoxic effect at a fixed dose of statin may, however, differ substantially from patient to patient as a result of a patient's characteristics, such as increased age, renal or liver impairment, hypothyroidism, metabolic muscle disease, or concomitant use of either other drugs with myotoxic effects (fibrates, niacin) or drugs that inhibit cytochrome P450 (CYP)-mediated clearance of statins.[20] For example, atorvastatin, simvastatin and lovastatin are extensively metabolized by CYP3A4 and fluvastatin by CYP2C9, whereas pravastatin is not metabolized.[21] Thus, problems with myotoxic effects may depend on the co-administration of the relevant CYP inhibitors, as well as the genetically determined variability of CYP activities.

From 1% to 3% of those who take statins will experience a dose-related rise in levels of the hepatic enzyme, alanine aminotransferase (ALT) and aspartate aminotransferase (AST). However, the incidence of severe transaminitis (rise in ALT

to 10 times the upper limit of normal) is about 0.1%, with no differences among the statins.[18]

Overall, an increasing body of evidence supports the safety and tolerability profile of statins, and the potential hazard of lipid-lowering with statins is considered to be extremely small in relation to the clear benefits.[18,22] Despite initial concerns that statins might increase the risk of non-cardiovascular mortality and cancer, recent meta-analyses provide reassurance that statin therapy does not increase the risk.[22,23]

1.2.3 Clinical aspects: effect on cardiovascular outcomes

In the 1990s five landmark, large, randomized, placebo-controlled trials demonstrated the benefits of statins on cardiovascular outcomes among patients with established CHD (secondary prevention) and those at high risk of developing such disease (primary prevention), regardless of cholesterol level. The 4S trial in 1994[4] established the importance of treating the hypercholesterolaemic patient with CHD. CARE,[24] another secondary prevention trial, showed the benefit of treating patients with cholesterol levels that are within normal limits, which was confirmed by the LIPID trial.[25] The first primary prevention trial, WOSCOPS,[26] showed the benefit of treating men at high risk for hypercholesterolaemia that was confirmed in the AFCAPS/TexCaps trial,[27] which included extended subgroups of women, elderly people aged up to 73 years and people with normal cholesterol levels.

Still there has been concern about the effectiveness in under-represented subgroups. The Heart Protection Study (HPS)[28] randomized more than 20 000 high-risk patients, and extended the knowledge of the benefits of statins in reducing CVD events in previously under-represented subgroups such as women, elderly people (up to 80 years of age), people with diabetes, and among individuals with below-average cholesterol levels. The primary prevention trials ASCOT-LLA[29] and CARDS[30]

showed the benefit in special high-risk groups of people with hypertension and diabetes. At the end of 2002, the result of PROSPER,[31] the first randomized controlled trial of the effects of statin treatment that specifically targeted elderly people (aged 70–82 years), stated the benefits for mortality from coronary heart disease (CHD) among elderly people, at least for secondary prevention.

The more recent statin trials (PROVE-IT, phase Z of the A to Z, TNT and IDEAL),[32-35] all of which are comparative statin trials, have tested whether patients with established CHD would derive more benefit from higher-dose 'aggressive' statin therapy. These trials show similar trends: high-dose statins (80 mg atorvastatin/simvastatin) will most probably reduce cardiovascular events in this high-risk patient category, at least in the long term.[36] However, there is an increase in incidence of adverse effects with higher doses.[37-39] For example, the number needed to treat (NNT) for the prevention of one treatment-related adverse event (persistent liver enzyme elevations) balanced the NNT for prevention of one CVD event in a recent 'high-dose trial' that compared 10 mg and 80 mg atorvastatin in patients with established CVD.[34]

In summary, the statins seem to produce similar relative risk reductions in CVD events, irrespective of prior history of CVD, age, gender and initial cholesterol levels.[22] Furthermore, a meta-analysis concluded that the relationship between the absolute LDL-C reduction and proportional reductions in the incidence of CVD events seems to be linear. Consequently, statin therapy can reduce the 5-year incidence of CVD events (including coronary events and/or stroke) by about a fifth for every reduction in LDL-C of 1 mmol.[22] The reduction in CVD events is translated into a significant reduction in cardiac and all-cause mortality in patients with or without CVD.[22,40]

To judge the absolute benefits (risk reduction) of statin therapy, however, the individual baseline risk has to be taken into account. Thus, the higher the baseline absolute risk for a CVD event, assessed from prior atherosclerotic disease, diabetes, blood pressure, smoking, age and gender, as well as cholesterol level, the larger the benefit (risk reduction) in absolute terms. Treatment of those who are at most risk will bring the most benefit; treatment of those who are not at high risk of CVD may expose patients who would not benefit much from therapy to its adverse effects.

1.3 Structural determinants for the prescription of LLDs in Norway

1.3.1 Guidelines on cholesterol management in clinical practice

Before the statin landmark trials, guidelines recommended LLDs (resins, nicotinic acid) only in individuals with TC levels above 8 mmol/L.[41,42] However, in Norway clinical guidelines for cholesterol management have been updated continuously as new evidence from large statin trials has emerged, in accordance with European guidelines[43-48] (Figure 3). The secondary prevention trials instigated guidelines recommending statins in patients with established CHD, who did not achieve target cholesterol levels (TC $\leq$ 5.0 mmol/L and/or LDL $\leq$ 3.0 mmol/L) by dietary and/or lifestyle intervention alone.[43,49] In primary prevention, individuals with high cholesterol levels, such as those with TC $\geq$ 8.0 mmol/L, were still considered to be eligible for LLDs. In addition, and in agreement with the evolving evidence of the benefits of statins in primary prevention, judgement of baseline CHD risk taking into account coexisting cardiovascular risk factors, now replaced assessment of elevated cholesterol as a single risk factor in targeting LLD therapy for primary prevention.[44,50]

Figure 3. Major statin trials and guidelines on their use in CVD prevention.

European guidelines 1st. Joint Task

Secondary/primary prevention:

Dietary therapy as the main form of treatment in patients at high rsik

Awaiting results of ongoing statin trial

1st treatment recommendation. Norwegian Medicines agency

Secondary prevention (CHD): TC> 5.5 (4S)

Primary prevention: Persistent LDL>5 and other risk factors or isolated hypercholesterolemia (persistent TC>8 or LDL>6

Intensive attention to dietary therapy

European guidelines 2nd. Joint Task

Secondary prevention (CVD): Aim: TC> 5 and LDL>3 (CARE)

Primary prevention: Absolut CHD risk (Framingham) >20% for a CHD event. Aim TC<5 and LDL<3 (AFCAPS, WOSCOPS)

2nd treatment recommendation. Norwegian Medicines agency

Concurrent to European guidelines

Europ.guidelines 3rd. Joint Task

New:

-Secnndary prevention: diabetes 2=secondary prevention Aim: TC<4.5 and LDL<2.5 (HPS)

-Primary prevention; From CHD to CVD prevention: SCORE >5% for fatal CVD event. Aim: TC<5 and LDL<3

3rd treatment recommendation. Norwegian Medicines agency New:

-Secndary prevention: diabetes 2=secondary prevention Statins to all with TC>3.5 (HPS) ?

-Primary prevention; Framigham or SCORE.

Timeline: 1994 · 1995 · 1996 · 1997 · 1998 · 1999 · 2000 · 2001 · 2002 · 2003 · 2004 · 2004-2006

	4 S (n=4444)	WOSCOPS (n=6595)	CARE (n=4159)	AFCAPS/Tex CAPS (n=6605)	LIPID (n=9016)	HPS (n=20 536)	PROSPER (n=5804)	ASCOT-LLA (n=10305)	CARDS (n=2838)	Comparative High-dose trials
	Secondary prevention elevated TC	Primary prevention elevated TC	Secondary prevention average TC	Primary prevention average TC	Secondary prevention average TC	Prim/Sec. Prevention	Prim/sec. Prevention	Primary prevention with hypertention	Primary prevention with diabetes 2	Secondary prevention
	Simvastatin 20-40 mg	Pravastatin 40 mg	Pravastatin 40 mg	Lovastatin 20-40 mg	Pravastatin 40 mg	Simvastatin 40 mg	Pravastatin 40 mg	Atorvastatin 10 mg	Atorvastatin 10 mg	80 mg simvastatin/ atorvastatin versus normal dose
	35-70 years. 19% women	45-64 year old men	21-75 years. 14% women	45-73 years 15% women	31-75 years 17% women	40-80 years 28% women	70-82 years 52% women	40-79 years 19% women	40-75 years 32% women	
	Study adds: benefit 2. pevention, elevated TC	Study adds: benefit 1. prevention, elevated TC	Study adds: benefit 2. prevention average TC	Study adds: benefit 1. prevention, average TC, women, elderly included	Study adds: emphasize (CARE) benefit 2. prev, broad range of initial TC	Study adds: benefit irrespective of CVD morbidity, age, gender, diabetes, initial TC	Study adds: benefit elderly, at least secondary prevention	Study adds: benefit 1. prevention hypertensives (high baseline risk)	Study adds: benefit 1. prevention with diabetes 2 (high baseline risk)	Study adds: The lower the better ?

From: [4,24-35,43-48]

The Framingham risk model was recommended as a multifactorial risk assessment tool to identify individuals at high CHD risk, and statins were recommended in individuals with TC above target in whom multiple risk factors result in a risk ≥ 20% of having a CHD event over the next 10 years at current age or when projected to the age of 60 in younger individuals (Framingham risk model, see 1.3.2 for details).

Since that time, large trials (HPS, PROSPER)[28,31] have extended our knowledge of the benefit of statin therapy to broader populations, such as elderly people and people with diabetes, and among individuals with below-average cholesterol levels. Accordingly, in 2003 new European guidelines on CVD prevention were published.[48] With reference to the HPS trial, people with diabetes should now be considered as candidates for secondary prevention, and lipid goals for secondary

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prevention have been lowered (TC: 4.5 mmol/L, LDL-C: 2.5 mmol/L). Furthermore, to identify high-risk individuals in the primary prevention subgroup, the European guidelines recommend the recently developed SCORE (Systematic Coronary Risk Evaluation) risk model as a tool in everyday practice (see 1.3.2 for details).[51] Accordingly, in those with TC above target values of 5 mmol/L, LLDs for primary prevention are recommended in those with a 10-year risk of *fatal* CVD of 5% or more (SCORE ≥ 5%) at current age or projected to the age of 60 in younger individuals, with no upper age limit for primary prevention.[48] The European guidelines claim to be a framework for the development of national guidelines; adaptations can be made to reflect practical, economic and medical circumstances in different countries.

Accordingly, the most recently published guidelines in Norway (2003) now suggest the use of either the Framingham or the SCORE risk model as a risk assessment tool for clinicians in practice, to target individuals for primary prevention intervention.[45] However, in Norway there are concerns about the predictive accuracy of the SCORE risk model, when applied on a Norwegian population. For this reason, the Norwegian Society of Cardiology (NSC) has not yet given their support to the new European guidelines.[52]

1.3.2 Cardiovascular risk assessment models

Multifactorial risk models are now recognized as essential in efficiently identifying individuals at high CVD risk, and in targeting individuals for intervention to prevent CVD as follows.

Until recently, use of the Framingham risk prediction model was synonymous with cardiovascular risk assessment in the European and Norwegian clinical guidelines for lipid management. [44,47] The updated versions of the Framingham risk model is based on data from individuals aged 30-74 years attending the Framingham

Heart Study, and who had their first examination in the period 1968-75.[53,54] From the experience of this group during a 12-year follow-up period, risk models estimating the risk of having CVD events over the next 10 years have been produced, that reflect the approximate combined impacts of the individual's age, gender, TC and HDL, systolic or diastolic blood pressure, and, in addition, the presence of diabetes mellitus, current smoking and signs of left ventricular hypertrophy.[53,54] Risk models are developed for several CVD end-points, separately and combined.[53] However, the most commonly used model has been the 'classical' model by Anderson, estimating the risk of having the first fatal or non-fatal CHD event.[54]

The Framingham risk model was, however, developed in a white American middle-class sample, which has raised concerns about whether these functions can be generalized to other populations. There are several reports indicating that this model is systematically overestimating the risk in Mediterranean populations,[55-57] as well as in populations from western and northern Europe.[58-61]

The European Society of Cardiology and the Joint Task Force of European Cardiovascular Disease Prevention therefore instigated the development of a risk estimation model, based on a large pool of representative European datasets, which would capture the regional variation in risk. The SCORE risk model is derived from datasets from 12 European cohort studies, mainly carried out in general population settings.[51] The Norwegian data included in the SCORE risk model were collected in the period 1974–78 with follow-up to 1994. The model estimates the 10-year risk of an individual having a fatal CVD event, on the basis of age, gender, TC concentration, systolic blood pressure and current smoking status. Thus, the assessment of baseline risk is now based on the risk of having any type of fatal CVD event, rather than CHD events alone, as it is with the Framingham model. With the SCORE risk model the

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threshold for being at high risk is defined by European guidelines as a 10-year risk $\geq 5\%$ of having a fatal CVD event, instead of the previous $\geq 20\%$ of having a fatal or non-fatal CHD event as assessed by the Framingham risk model.[48] This may agree more with current evidence because lipid-lowering with a statin lowers the risk not just of CHD events but also of ischaemic strokes.[22]

Separate SCORE risk models have been developed for high- and low-risk European populations. Norway is classified as a high-risk country. As age is a major determinant of CVD risk, and the age ranges of the cohorts were somewhat heterogeneous, the calculation of model fit was limited to the age group 45–64 years.[51]

1.3.3 Reimbursement for LLDs in Norway

In Norway the cost of LLDs is reimbursed by the National Insurance Administration, through the reimbursement scheme.[62] Until recently LLDs had been reimbursed for individuals with symptomatic CVD (secondary prevention), and for primary prevention in patients with familiar hypercholesterolaemia or among those with a TC that stays at 8 mmol/L or higher after a year of dietary intervention.[63] The reimbursement regulations have not been updated for several years, and do not agree with recent evidence, which has been an area of criticism.[64] Thus, clinical guidelines recommend a more up-to-date use of LLDs for primary prevention, in particular by the assessment of treatment eligibility through a multifactorial approach.[44,45] However, considering the lack of regulations and control systems for ensuring adherence to conditions for reimbursements for LLDs, use of all LLDs has been reimbursed in practice, and few doctors seem to follow the conservative reimbursement terms in medical practice.[62,65] In June 2005, however, updated

reimbursement terms for LLDs were launched in Norway, to concur with clinical

guidelines for primary prevention.[66]

After the increasing consumption of LLDs, the reimbursement cost has

increased substantially over the last 10 years. This increasing expenditure has been of

great concern. The total public spending on drugs in 2005 was 16 billion Norwegian

kroner (NOK) (1 Euro = 8 NOK), and the reimbursable drugs paid for by the National

Insurance Administration amounted to NOK 9.4bn. In 2005 the sales of LLDs

amounted to approximately NOK 0.8bn, about 10% of the total expenditure on

reimbursable drugs. However, the health authorities have introduced several

regulations to reduce cost, such as the 'index-price' system in 2003, the graded price

model and new reimbursement terms that demand the use of off-patent simvastatin as

the preferred drug in June 2005. Accordingly, from 2004 to 2005 the relative cost of

LLDs decreased by about 17%, despite the 19% increase in defined daily doses

(DDDs).[5]

1.4 Sources of information on LLD use in the general population in Norway

The major sources of information on LLD use in the general population include

wholesale statistics, prescription data and self-reported use from questionnaires in

health surveys.

1.4.1 Wholesale statistics

Since 1977 a statistical presentation of the drug consumption in Norway, as a whole

county and a county level, has been published annually, based on total sales from

wholesalers to pharmacies and hospitals and sales outside pharmacies.[5] Currently the

figures are prepared and published by the Norwegian Institute of Public Health.

Wholesale statistics give a complete picture of overall sales, including prescription

and non-prescription drugs, and the statistical material is presented according to the Anatomical Therapeutic Chemical (ATC) classification system, with DDDs and NOK as units of measurement.[67] The sales data are presented as the number of DDDs per 1000 inhabitants per day, which offers an opportunity to study time trends and regional variations in drug consumption, as well as a basis for a rough estimation of the proportion of the population on therapy with particular drugs. This last estimate presupposes, however, agreement between the DDD and the actual prescribed dose.

Until recently, wholesale statistics have been the only available source of information on LLD use in the general Norwegian population. They may, however, have several limitations as a measure of actual drug consumption in a population. For example, drugs sold by wholesalers are not necessarily dispensed, and drugs dispensed by pharmacies may not be used. Sales statistics do not distinguish between drugs sold to individual patients and those sold to hospitals, and patients may have their medication dispensed outside their county of residence. However, LLDs are sold in such high amounts that pharmacy stocks would constitute only a minor error in LLD sales. LLDs are reimbursed as chronic drug therapy and dispensed mainly to patients in primary care. Thus, LLD sales can be assumed quite reasonably to reflect the trends in LLD consumption in a region.

1.4.3 Population-based health surveys

In general, self-reported use of drugs obtained from questionnaires or interviews, as part of a health survey, is commonly used as a source of drug use in the population.[68] Depending on the comprehensiveness of the studies performed, such surveys allow information on drug use in individuals, in relation to other relevant variables, such as sociodemographic variables, and information on health status and risk factors, including clinical measurements.

The Norwegian Institute of Public Health has performed systematic health screening in Norwegian counties since the 1970s.[69,70] The primary objectives of this screening were to monitor and prevent CVD. However, in the municipality of Tromsø, extended repeated surveys, including clinical examinations (the Tromsø Study), have been performed in the same population five times. The initial surveys included questions on drugs used for high blood pressure only. Since then the questions on drug use have been changed and developed.[71] From 2000 to 2001 standardized questions on LLDs were included in questionnaires in successive surveys, including the health surveys used in this thesis: the health survey in the counties Oppland and Hedmark (the OPPHED Health Study, 2000–2001) and the fifth survey in Tromsø municipality (the Tromsø Study V, 2001). This design includes specific questions on the use of LLDs, followed by an open-ended question for which the participants are asked to write down the proprietary name of all drugs used in the preceding 4 weeks (see Appendices A and B).

1.4.4 Prescription data: the Norwegian Prescription Database (NorPD)

A growing need for more detailed information about drugs prompted the establishment of a national prescription register in Norway. [72,73]

The main purposes of the register, as defined in authoritative regulations, are to collect and prepare data on drug use in humans and animals in order (translated into English by Ingeborg Hartz):[74]

1. To describe drug use in the population, including changes over time.

2. To form a basis for and promote research into the safety and effectiveness of drug use.

3. To provide the authorities with an administrative tool to assure high-quality prescribing, in addition to providing a tool for supervision, control and planning at a non-individual level.

4. To give the prescribers a basis for reviewing their own prescriptions, as part of an audit to improve quality of prescribing.

Thus, from 1 January 2004, all pharmacies in Norway have been obliged, by law, to submit electronic data on all prescriptions to the Norwegian Institute of Public Health.[74] The NorPD includes prescription data from the total population (4.6 million) in Norway from 2004 onwards. The identity of patients and prescribers has been encrypted, but each record contains a unique person identifier, derived from the Central Population Registry (CPR), which makes it possible to identify all prescriptions over time for individuals. The NorPD contains information from all prescription drugs, whether or not reimbursed, dispensed at pharmacies to individual patients living outside institutions.

1.5 Cholesterol management: evaluation of LLD use in individuals

An evaluation of the extent to which the observed increase in LLD consumption can be reflected in proper cholesterol management for the treatment of eligible patients presupposes individualized data on LLD use linked to clinical information on cardiovascular morbidity and risk factors.

In Norway, such studies have focused on LLD use among patients who are eligible for secondary prevention, based on information from their general practitioner's (GP's) surgery and hospital records.[75-80] At the time that statins entered the market, a cross-sectional study from 31 Norwegian GP surgeries in 1994–95 revealed that more than 90% of the patients with established CVD had TC levels above the recommended 5.0 mmol/L, less than 20% were on LLDs and only a

minority of those on treatment had achieved the recommended TC goal.[75] In 1996–97 a repeated survey revealed that the proportion on LLDs increased to 55%, and the greater proportion of statin use reflected a 15% reduction in TC level compared with 2 years earlier.[78] In parallel, initiation of statin therapy during hospitalization for acute myocardial infarction (MI) increased steadily in the 1990s.[76,79,80] However, there is still suboptimal cholesterol management of this group eligible for treatment: only 50% of the LLD users achieved the recommended TC target of 5 mmol/L at their first outpatient review, similar to observations among LLD users from GPs.[77,79] Patients were maintained on starting doses of statins or on doses that had not been titrated to levels associated with reduced cardiovascular morbidity and mortality.[77] Despite increasing use of LLDs for secondary prevention, most of those eligible for secondary prevention had raised lipid levels.[78]

These Norwegian studies confirm and expand the observations of cholesterol management for secondary prevention in other European countries.[81-85] In the period 1995–2000, there have been improvements in cholesterol management for secondary prevention, as observed among MI patients.

The EUROASPIRE I and II studies found that, among patients with acute MI aged < 70 years, the percentage receiving statins during the first 6 months after discharge increased from 17% in 1995–96 to 59% in 1999–2000.[81] The proportion with a raised TC (> 5 mmol/L) decreased from 85% to 60%. However, overall most CVD patients still have raised TC levels, and only half of the LLD users achieved the TC targets.[81] Both studies involved selected hospitals that were willing to participate, and an even more suboptimal management of secondary prevention could be expected in Europe as a whole. In comparison, a Danish, nation-wide, population-based study using health registries (patient registry and prescription registry) that involved all hospitals

revealed a similar trend: proportion of patients aged < 70 years using statins within 6

months of discharge was 23% in 1995–96, 58% in 1999–2000 and 78% in 2002.[85]

'Healthy' individuals, however, constitute the majority of the population, who

are not necessarily registered in GP surgeries or hospital records. Thus, including the

primary prevention subgroup, an evaluation of cholesterol management in the total

population presupposes data from population screening. Such evaluations have, until

recently, been lacking in Norway, and population-based reports on cholesterol

management with LLDs for primary prevention are scarce in other European

countries. As observed for secondary prevention, there seems to be a gap between the

actual and the recommended levels of LLD use for primary prevention, as evaluated

in Dutch and British populations.[86-91] Direct comparisons between analyses are

difficult, because of the different age distributions in the population samples studied

In addition, in British and Dutch populations cholesterol management with LLDs for

primary prevention is evaluated according to a varying set of prevailing national

intervention thresholds, which are issued after taking into account population

implications in terms of cost and workload on the health-care system.[92] For example,

until recently, the Joint British guidelines recommended intervention among

individuals with a 10-year CHD (Framingham) risk ≥ 30%,[92-94] and Dutch guidelines

restrict LLDs to middle-aged individuals who exceed age- and gender-specific cut-off

points, with risk ranging from 25% to 40%.[89-91] As a result, the proportion eligible for

primary prevention varies according to different thresholds set, and therefore

proportions of eligible individuals treated would vary. In the 1998 Health Survey of

England, 3.8% and 0.4% of all 30- to 70-year-old asymptomatic men and women

were eligible for LLDs at a risk threshold of 30%, of whom less than 3% were on

LLDs,[88] and in a Dutch population survey 6% of all asymptomatic 30 to 70 year olds

in the Netherlands were eligible, of whom 44% were treated.[90] However, recent Joint

British guidelines (2005) now recommend LLDs in individuals with a 10-year CHD

(Framingham) risk $\geq$ 20% and a TC > 5 mmol/L, which concurs with European and

Norwegian guidelines.[94] According to this intervention threshold, 21% of all English

asymptomatic men and women aged 30 and older are eligible for LLDs, of whom 8–

9% had been treated, as revealed by the 2003 English Health Survey.[86]

2 Aims of the thesis

The sales of LLDs in Norway have increased dramatically since statins entered the market in the early 1990s, but information on LLD use in individuals in the general population has been lacking in Norway.

The aims of this thesis are as follows:

1. To study cholesterol management with LLDs in a general population, according to the criteria for LLD use in the guidelines, comparing:
   – the present situation with prevailing guidelines
   – the present situation with a future 'scenario' of implementation of European SCORE-based thresholds for primary prevention

2. To study general aspects of LLD use, which may contribute to regional differences in LLD sales.

3 Study population and methods

3.1 Sources of data

This thesis is based on data from the Tromsø Study V, the OPPHED Health Study and the Norwegian Prescription Database (NorPD).[72,95,96]

3.1.1 The Tromsø Study V

The Tromsø Study is a prospective follow-up study of inhabitants in the municipality of Tromsø, Norway, situated at 69°N (current population 63 000), and has been repeated five times since 1974.[95] The fifth survey was conducted in 2001 by the Institute of Community Medicine, University of Tromsø, in collaboration with the Norwegian Institute of Public Health, and was primarily designed to explore risk factors, chronic diseases and drug use in individuals.[95]

In 1994 (the fourth Tromsø study), all inhabitants aged 55–74 years and 5–10% of samples in other age groups were invited to an extensive examination (attendance rate 77%). Of these, all those still residing in Tromsø in 2001 were invited to the fifth survey ($n = 6,961$). In addition, all inhabitants aged 30, 40, 45, 60 and 75 years in 2001 were invited, making up a total of 10,353, of whom 8,130 attended the screening (attendance rate 79%; see Table 2 for details).

All the people invited were initially contacted by mail with a questionnaire enclosed in the letter of invitation. The questionnaire included questions on sociodemographic factors, symptoms, diseases, family history of CVD, smoking and dietary habits, physical activity at leisure and drug use (see Appendix A for details, for those aged above and below 70 years). The questionnaires were collected at the following visit, where height, weight and blood pressure were measured and non-fasting blood samples were collected, after a standardized procedure similar to previous

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screenings.[97] All participants were handed a stamped, addressed envelope with a second questionnaire, which they were asked to complete at home and return in the mail (Appendix A).

Table 2. Age- and gender-specific attendance rate among 10,353 participants invited to the Tromsø Study V

| Age | Invited | | Attendants | |
| | men | women | men | women |
	N	N	n (%)	n (%)
30-39	683	741	283 (41.4)	423 (57.1)
40-49	1006	1079	614 (61.0)	762 (70.6)
50-59	392	770	363 (92.6)	722 (93.8)
60-69	1381	1603	1248 (90.4)	1463 (91.3)
70-79	1012	1310	885 (87.5)	1099 (83.9)
80+	163	214	118 (72.8)	150 (70.1)
Total	4636	5717	3511 (75.7)	4619 (80.8)

3.1.2 The OPPHED Health Study

In 2000–2001 the Norwegian Institute of Public Health performed a health survey in the two neighbouring counties, Hedmark and Oppland, known as the OPPHED Health Study.[96] All individuals aged 40, 45, 60 and 75 were invited to a health screening; they numbered 8,754 from Hedmark and 8,592 from Oppland. A total of 10,598 (61%) of these individuals attended the screening (see Table 3 for details), which consisted of self-administered questionnaires (Appendix B) and clinical measurements, similar to the Tromsø Study V. The OPPHED Health Study also included individuals aged 30 years, but these were not included in our analysis.

Table 3. Age- and gender-specific attendance rate among 10, 598 participants invited to the OPPHED Health Study

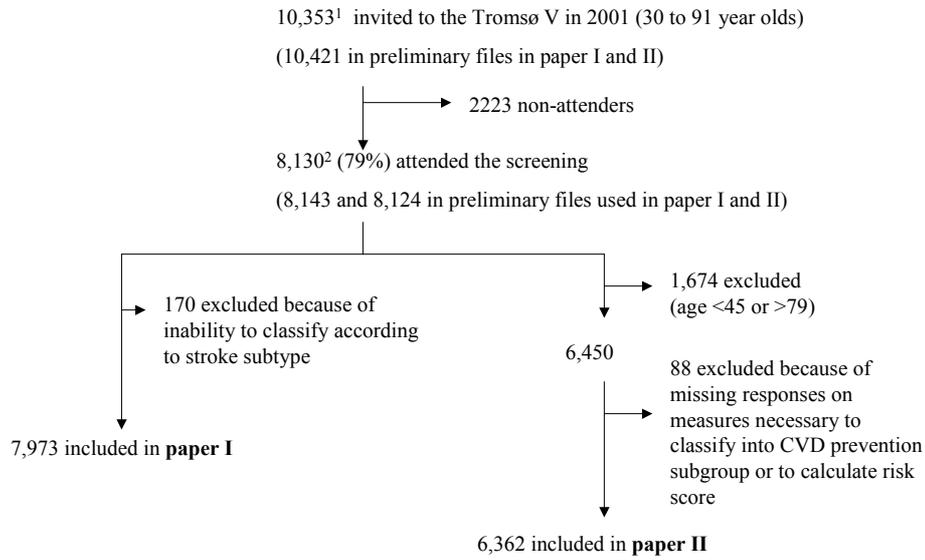|	Invited		Attendants	
Age	men	women	men	women
	N	N	n (%)	n (%)
Hedmark				
75	771	903	487 (63.2)	520 (57.6)
60	985	953	659 (66.9)	673 (70.6)
40+45	2556	2586	1367 (53.5)	1666 (64.4)
Total	4312	4442	2513 (58.3)	2859 (64.4)
Oppland				
75	654	891	411 (62.8)	468 (52.5)
60	885	989	612 (69.2)	745 (75.3)
40+45	2630	2543	1357 (51.6)	1633 (64.2)
Total	4169	4423	2380 (57.1)	2846 (64.4)

3.1.3 The Norwegian Prescription Database

The NorPD contains information from all prescribed LLDs dispensed at pharmacies to individual patients.[72,73] The information included in the register is collected monthly from all pharmacies, and includes all relevant data on the prescription form, such as: patient's gender, age and place of residence; prescriber's gender, age and speciality; pharmacy identifier; date of dispensing; and drug information (proprietary name, package size, number of packages, ATC code, DDD, price, code for reimbursement). [72,73]
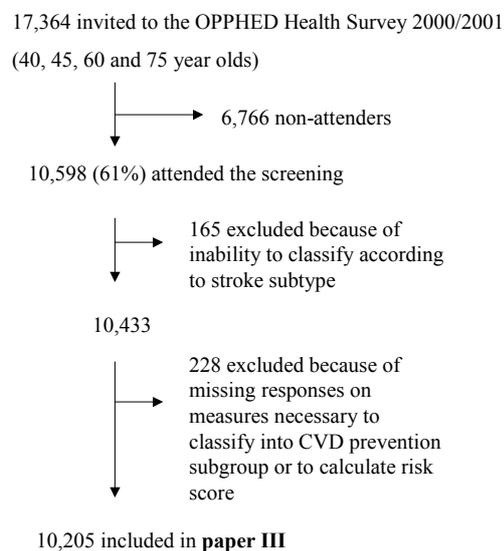
3.1.4 Study population and design

Papers I and II include participants from the Tromsø Study V, whereas paper III includes participants in the OPPHED Health Study, as summarized in Figure 4. Papers I–III all have a cross-sectional design. In paper IV we retrieved data from the NorPD on patients who had received at least one prescription of a statin (ATC-group C10AA) during 2004 in the counties Hedmark, Oppland and Troms. In total, 40,143 statin users were included in our analysis.

Figure 4. Study populations in papers I–III.

10,353[1] invited to the Tromsø V in 2001 (30 to 91 year olds)

(10,421 in preliminary files in paper I and II)

→ 2223 non-attenders

8,130[2] (79%) attended the screening

(8,143 and 8,124 in preliminary files used in paper I and II)

170 excluded because of inability to classify according to stroke subtype

1,674 excluded (age <45 or >79)

6,450

88 excluded because of missing responses on measures necessary to classify into CVD prevention subgroup or to calculate risk score

7,973 included in **paper I**

6,362 included in **paper II**

[1] The number of invited people are reported to be 10,421 in paper I and II due to incompleteness in our preliminary files (68 individuals in preliminary invitation-file excluded in final version)

[2] The number of attendants are reported to be 8,143 in paper I and 8124 in papaer II, due to inclompleteness in our preliminary files

17,364 invited to the OPPHED Health Survey 2000/2001

(40, 45, 60 and 75 year olds)

→ 6,766 non-attenders

10,598 (61%) attended the screening

→ 165 excluded because of inability to classify according to stroke subtype

10,433

→ 228 excluded because of missing responses on measures necessary to classify into CVD prevention subgroup or to calculate risk score

10,205 included in **paper III**

3.2 Exposure variables

In papers I–III, information on exposure to LLDs is based on questions in the main questionnaire for the Tromsø Study V and the OPPHED Health Study.

The questionnaires (see Appendices A and B) display specific and open-ended questions on the use of LLDs in the Tromsø Study V and the OPPHED Health Study, which were similarly phrased. Thus, in addition to ticking off the categories yes/previously/never on current use of LLDs (specific drug question), the participants were asked to report the proprietary names of all drugs used during the preceding 4 weeks (open-ended questions). A database was then used to register these proprietary drug names. The ATC system, version 2000, was included in this database, and each proprietary name reported was given the corresponding ATC-code at the substance level (fifth level of ATC, 7 digit code).

In papers I and II, participants reporting either a proprietary name of LLD (ATC-group C10) and/or current LLD use were included as LLD users in the analysis.

In paper III defined LLD users were restricted to those participants answering 'yes' on current use of LLDs.

In paper IV information on exposure to statins was based on prescription data from the NorPD. We retrieved the data from the NorPD on patients who had received at least one prescription of a statin (ATC-group C10AA) during 2004 in the counties Hedmark, Oppland and Troms.

3.3 Statistical methods

The statistical analyses were performed using the SAS software package, version 8 (papers I and II) and the Statistical Package for Social Sciences Programme (SPSS),

version 10 (paper III) and version 12 (paper IV). Descriptive statistics, and univariate and multivariate analyses were performed.

Age adjustments of current and recommended proportions on LLDs in total age groups (paper II) and total period of prevalence of statin use (paper IV) were carried out using the direct method, with the Norwegian population as a standard.

In paper III categorical variables (presence of CVD morbidity, proportions with Framingham risk score > 20%, proportions of LLD use in the primary and secondary prevention subgroup and proportions of LLD users achieving the TC goal) were compared using the chi-squared (χ^2) test. Continuous variables were compared using *t*-tests for variables with a normal distribution (TC in paper I, TC and systolic blood pressure in paper II) or non-parametric Mann–Whitney tests for variables with a skewed distribution (time since MI and angina diagnosis in paper I, MI score in paper III).

In paper I, the associations between LLD use and sociodemographic factors, CVD risk factors and morbidity were presented as odds ratios with 95% confidence intervals, using logistic regression analyses. First univariate (adjusted for age), then multivariate to analyse predictors of use, in general adjusted for other co-variates.

4. Summary of papers and main results

Paper I

Whom are we treating with lipid-lowering drugs? Are we following the guidelines? Evidence from a population-based study – The Tromsø Study 2001. Eur J Clin Pharmacol 2004;60;643–9.

The main purpose of this study was to describe cholesterol management with LLDs in a general population according to the criteria for LLD use described in prevailing national guidelines for cholesterol management. Overall, the majority of our study population had a TC > 5 mmol/L – 79% of all men and 84% of all women, respectively. About half of the secondary prevention subgroup reported being on LLDs, although 60% of all men and 77% of all women had TC levels above the recommended target. Younger age predicted LLD use for secondary prevention in both genders, and LLD users reported having had an MI more recently than non-users. In the primary prevention subgroup (no CHD), 47% had raised TC levels, defined as individuals with a risk condition (hypertension and/or diabetes) and TC level above the target of 5.0 mmol/L, and healthy individuals with TC levels ≥ 8.0 mmol/L. In this group, who are eligible for primary prevention, 8.0% of the women and 7.4% of the men reported LLD use. Hypertension, diabetes, increasing BMI, decreasing level of education and older age were predictors for LLD use in primary prevention among women, whereas hypertension and diabetes were the only significant predictors among men. Of all those reporting LLD use, only a third achieved the recommended TC goal. This study concludes that there is a large gap between guidelines for cholesterol management and guidelines for clinical practice.

Paper II

Does implementation of the European guidelines based on the SCORE model double the number of Norwegian adults who need cardiovascular drugs for primary prevention? The Tromsø Study 2001. Eur Heart J 2005;26:2673–80.

Paper II describes the implications of implementing European SCORE-based intervention thresholds for the use of cardiovascular drugs in primary prevention in a Norwegian population. This thesis, however, focuses on implications for LLD use.

In the primary prevention subgroup of the 45–64 year olds, recommended LLD use would be markedly higher only in men: 40% compared with 8% on current medication. Among women, recommended and current proportions on LLDs were 3% and 7%, respectively. Among the 65–79 year olds, over 80% would be eligible for LLDs in both sexes, compared with current treatment rates of < 10%. In total, 51% of all men and 30% of all women aged 45–79 years would be candidates for primary prevention with LLDs, compared with 7% and 5% on current medication. This study concludes that implementation of European guidelines, recommending intervention threshold based on the SCORE high-risk model, could imply a sixfold increase in the number of Norwegian adults on LLDs for primary prevention (from 6% to 38%). Major contributors would be more frequent use in men and elderly people, in particular.

Paper III

Why do sales of lipid-lowering drugs vary between counties in Norway? Evidence from the OPPHED Health Study 2000–2001. Scand J Prim Health Care 2006;25:115–21.

The main purpose of paper III was to explore factors that might explain varying sales of LLDs in the neighbouring counties Oppland and Hedmark. Factors studied were treatment eligibility, treatment frequency in treatment-eligible subgroups and treatment intensity in terms of achievement of the TC goal. In this study we found no inter-county differences in the prevalence of CHD or diabetes. In addition, similar TC concentrations and risk level (Framingham risk score and the Norwegian MI score) in the primary prevention subgroup should imply similar proportions eligible for LLD therapy. In the primary prevention subgroup, among men in particular, a large part of those reporting not to be on LLD therapy had a Framingham risk score above the $\geq$ 20% limit set by guidelines in both counties: a third of all 60 year old men, increasing to about 80 % of all 75 year old men. Corresponding figures among women were 5 and 10%, respectively.

There was no difference in prevalence of LLD use in the secondary prevention subgroup, but LLD use among men in the primary prevention subgroup was higher in Hedmark compared with Oppland: 6.3% and 4.1%, respectively ($p < 0.05$). The same tendency was seen among women. In both sexes, more LLD users in the primary prevention subgroup achieved the TC goal in Hedmark compared with users in Oppland ($p < 0.05$). This study concludes that a lower threshold for the initiation of LLD therapy for primary prevention, and a more intensive therapy with higher attainment of TC goals, are factors that probably contribute to differences in LLD sales between the counties.

Paper IV

Aspects of statin prescribing in Norwegian counties with high, average and low statin consumption - an individualised prescription database study. Submitted manuscript

Based on prescription data, the main purpose of paper IV was to explore different aspects of statin use in individuals, complementary to information attained from Norwegian health surveys. Thus, prevalences of use, dosing characteristics, choice of statin and continuity of therapy, were explored in individuals in counties with high, average and low statin consumption.

The high-consumption county had higher prevalence of statin use in all age groups. Atorvastatin accounted for 42–47%, simvastatin 37–40% and pravastatin the remaining 9–17% of users in the three counties. More users in the high-consumption county Hedmark were prescribed atorvastatin and simvastatin, whereas pravastatin constituted a larger proportion of all statin users in the other counties. The estimated PDDs for all statins were higher than the DDDs – up to twice the DDD for atorvastatin. The high-consumption county had the highest PDD for simvastatin (25.9 mg) and atorvastatin (21.9 mg), followed by average- and low-consumption counties. Accordingly, more users in the high-consumption county were prescribed simvastatin and atorvastatin in the upper range of available strengths, including 'high-dose therapy' (atorvastatin and simvastatin 80 mg). Continuity of treatment was similar, assessment by the number of tablets dispensed per day, demonstrated that the users retrieved statins corresponding to the use of a tablet a day in all counties.

By adding prescription data to previous knowledge on statin use from the latter surveys, this study concluded that higher prevalences of use, with a greater tendency towards statin use in primary prevention, higher PDDs with more statin users

achieving the TC target, and extensive use atorvastatin may be factors contributing to higher overall statin consumption.

5. Discussion

5.1 Methodological considerations

An overall goal in epidemiological research is to measure the value of a parameter, such as prevalence of LLD use, as accurately as possible. Whereas data from the NorPD cover electronic information on LLD use in the total population, the participants in the health surveys used in this thesis represent samples of a source population and the drug information is based on self-report.

How accurately the measured value of a parameter in such a study population reflects the 'true' parameter in the source population depends on the presence of errors. The internal validity refers to whether or not the results of a study are valid for the individuals being studied, and not the result of chance (random error) or systematic error (bias or confounding).[98] In general, the amount of random error will diminish, and the confidence interval surrounding the point estimate will be narrower, with increasing sample size. Hence, the first way to increase precision in epidemiological studies is to enlarge the size of the study population. Data from the NorPD cover prescriptions from the total population and the study populations in the health surveys used in this thesis were large, so problems with random error were considered to be small. However, division of the population into many strata, such as proportions of LLD users achieving TC goal according to age, gender and CVD morbidity status (paper III), may result in less precise estimates in each stratum. The amount of systematic error (bias) is, however, unaffected by sample size. Bias tends to be a greater problem in observational studies, due to an error in design or execution of the study, which produces results that are consistently distorted in one direction.[98] In the following section, the different types of bias relevant to our studies are discussed.

5.1.1 Selection bias

This type of bias is a distortion of the measurement of an estimate, which is the result of the selection of individuals who are not representative of the source population about whom conclusions are to be drawn.[98]

In the health surveys used in this thesis, there were no other selection criteria besides age. In the OPPHED Health Study all individuals in certain age groups in Hedmark and Oppland were invited to the screening. In the Tromsø Study V, samples from selected age groups were invited randomly by use of the personal identification number, in addition to participants in the Tromsø Study IV. Hence there is no reason to believe that the recruitment process has contributed to the invitation of individuals with a more unusual pattern of drug use or other health variables than in the source population. Thus, the main source of selection-bias in the studies based on data from health surveys is non-response, either non-attendance or missing response to single items on the questionnaire.

The overall attendance rate in the Tromsø Study V was 78% (Table 2, page 22), which was lowest in the youngest age group, but up to 86% in those aged 45–79 years (included in paper II). Analyses of the non-participants aged up to 44 years in the Tromsø Osteoporosis Study (TROST), which is a part of the Tromsø study, revealed no differences with regard to central lifestyle parameters, except that more non-participating men tended to be smokers.[99] In contrast, non-participants in older age groups were shorter, had a higher BMI (women), were more often smokers, and more often perceived their own health as bad compared with that of those attending both the Tromsø Study IV and the Tromsø Study V.[100] In addition, baseline bone mineral density was lower among the non-participants, which is a powerful predictor of general health status.[101] The possible 'healthy selection bias' may have resulted in

an underestimation of our cardiovascular risk factor levels and LLD use, because severe CVD itself might have prevented elderly people, who are most likely to be LLD users, from attending the screening. Furthermore, in the fifth survey all participants in the fourth survey (1994–95) who were still alive were invited. Selective survival may be present, especially among elderly people, contributing to an over-representation in the study of individuals with low cardiovascular risk factor levels and low LLD use.

In the OPPHED Health Study (paper III), the overall attendance rate among individuals included in paper III was below 60% (Table 3, page 23). Unfortunately, we do not have any direct information about the non-participants in the OPPHED Health Study. Although not directly comparable, the effect of increasing the attendance from 30% to 46% through reminders in the Oslo Health Study (2000–2001) resulted in somewhat higher prevalence estimates of diabetes, daily smoking and obesity, and poorer self-reported health in elderly people, with no change among younger individuals.[102 103] Although increased attendance rate had only minor effects on prevalence estimates, it revealed the same trend of 'healthy selection bias' as observed in the Tromsø study. The aim of paper III, however, was to compare possible contributing factors to higher total LLD sales in Hedmark and Oppland, and not to determine prevalence estimates. An underestimation of cardiovascular morbidity and LLD use might bias our comparisons between Hedmark and Oppland, if unequal underestimation were likely. As a result of similar attendance rates within each gender and age group compared, similar procedures for health survey invitation and screening, and similar rural/urban and population composition of the two neighbouring counties, however, we can assume equal underestimation of prevalence of cardiovascular morbidity and LLD use in the two counties.

The item response of attendees on use of LLDs was high in the health surveys

used in this thesis. Among the 8143 participants in the Tromsø Study V, only 3% (n

= 262) did not respond (missing) to the question on LLD use, and were included in

the analysis as non-users. Analysis of LLD use, excluding those with missing data on

LLD use, did not change the results significantly. In line with this, the response rate to

questions on LLD use in the OPPHED Health Survey was in the range of 92-99 % in

the age-categories included in our analysis.[104]

5.1.2 Information bias

Information bias is related to the accuracy of the information that is collected on

different variables, such as drug use and health status.

Observational studies frequently use self-reported data on drug use and health

status, and the quality of these data relies on both comprehension and interpretation of

the questions, as well as the ability of individuals to recall information accurately.

In general, the methodological literature on recall accuracy indicates that study

participants have difficulty remembering drug use from the distant past. Furthermore,

the type of question influences how well respondents answer questions about drugs,

and it appears that indication- or medication-specific questions invoke better recall

accuracy than open-ended questions.[68] Thus, the technique of using medication- or

diagnosis-specific questions, recall enhancers (such as photos) and two different types

of drug question has become 'state of the art' for collecting self-reported drug data.[68]

Apart from the use of recall enhancers, the drug use questions on LLDs in the health

surveys used in this thesis seem to comply with this 'state of the art', and can thus be

considered to be well phrased in order to improve the completeness of the self-report

on these drugs (see Appendices A and B). In addition, the participants were asked to

tick *current* use of these drugs, as well as to report the proprietary names of all drugs

used during the *preceding 4 weeks,* thus reducing the problem with recall accuracy that relates to memory of drug use in the distant past.

In the Tromsø Study V, of the 917 included as LLD users in our analysis in paper I, only 15 reported the proprietary name without ticking 'yes' on current use of LLDs. For this reason we can assume that inclusion of only those answering 'yes' in the OPPHED Health Study as LLD users in paper III did not contribute to severe underestimations of LLD use as a result of missed individuals reporting only a proprietary name.

Recall accuracy of self-reports of hormones or pregnancy-related exposures is validated in several studies, but studies validating self-reports of other drug classes, including cardiovascular drugs, are scarce.[68] However, in a Dutch study, validation of indication-specific questions on current use of antihypertensive drugs, with a similar question structure to those used in the Norwegian health studies, showed sensitivity of over 90%.[105] In general, the accuracy of self-reports of cardiovascular drugs, including antihypertensives and statins, appears to be good across the few published studies. This may be related to their use for CVD as a well-defined chronic condition, and not belonging to the 'socially undesirable chronic medications', such as antidepressants, that are underreported to a large extent.[106-111]

No validation has been performed in the health surveys with regard to self-report of LLD use. However, in the Tromsø Study V, 785 of 928 (85%) of those reporting current LLD use also reported a proprietary LLD in another part of the questionnaire, which consolidates the information on LLD use. Corresponding figures in the OPPHED Health Study were 81%.[104] The formulation of questions on morbidity and drug use in the questionnaire used in this study has, however, been used in other surveys performed by the Norwegian Institute of Public Health.

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Validation of questionnaire information from these comparable surveys has shown agreement with medical records for prevalent diabetes (96%), MI (81%), and current use of antihypertensives (97%), insulin (95%) and oral anti-diabetics (100%).[112,113] These results agree with other studies that show accurate recall of medical and drug use history for well-defined chronic conditions, including angina pectoris.[108,114]

5.1.3 Confounding

A simple definition of confounding would be the confusion, or mixing, of effects (from the Latin *confundere*, to mix together).[68,98] Thus, confounding occurs when the estimate of a measure of association between drug exposure and health status is distorted by the effect of one or several other variables. As cardiovascular morbidity and risk factor level, and presumably LLD, use increase with age, particularly among men, age and gender as important confounders needed to be addressed. Confounding is a particular kind of bias that can be controlled at the analysis level. In the current papers, confounding was addressed by using multivariate, age- and gender-specific analyses, and age standardization

5.1.4 Completeness of the prescription data from the NorPD

With regard to patients in nursing homes and hospitals, the NorPD receives figures on drug use at the institution level. Thus, prescription information may be missing for elderly people living in nursing homes. Prevalence of statin use in older age groups, as well as in the total population, may be underestimated. Furthermore, the NorPD do not reveal information on non-prescription drugs, which would make it unsuitable as a source of information about the use of certain drug groups, such as analgesics and laxatives. However, statins are prescription drugs, and information on statins dispensed to individuals living outside institutions can be considered complete. The

interpretation of prescription data as 'statin use' should take into account the fact that drugs dispensed from pharmacies may not be used.

5.2 Discussion of the main findings

5.2.1 Cholesterol management with LLDs – according to prevailing guidelines

Overall, the majority, 80%, of our study population had cholesterol levels > 5 mmol/L; less than 15% reported being on LLDs. Although this reflects cholesterol levels in an elderly sample, with 60% aged over 60 years of age, our findings of relatively high 'unfavourable' cholesterol levels are confirmed in population screening from other parts of Norway: as many as 80% already had 'unfavourable' TC levels at age 40–44 among men and 45–50 among women.[115] Furthermore, the Norwegian situation fits very well with observations from other European countries, such as England: repeated health screenings in 1998 and 2003 revealed that 70% of all adults (> 16 years) had cholesterol levels > 5 mmol/L.[86-88]

Norwegian guidelines on cholesterol management recommend intervention with LLDs in individuals at high risk, such as those with symptomatic CVD, and among asymptomatic individuals in whom multiple risk factors result in a high absolute baseline risk of developing symptomatic disease in the future. An individual with a number of mildly abnormal risk factors may be at a level of greater absolute risk than someone with just one high risk factor, such as a high cholesterol level. Therefore, a description of how well cholesterol, as a risk factor, is managed with LLDs in the population needs to be given in line with the presence of coexisting symptomatic disease and risk factors. In the following section, cholesterol

management in a secondary or primary prevention subgroup is discussed separately and in more detail.

Secondary prevention

In line with the increasing LLD sales in the 1990s, and after the introduction of statins to the Norwegian market, studies from general practice revealed that the proportion of people on LLDs for secondary prevention increased, with a greater proportion achieving the TC goal.[78] However, compared with recommendations, cholesterol management in this treatment-eligible subgroup was suboptimal in 1996–97: only 50% were on LLDs and 77% had TC levels above the target of 5 mmol/L.[78]

Since then, and up to 2000–2001, when health screening in Tromsø, Hedmark and Oppland took place, LLD sales have increased threefold, but there remains a corresponding gap in cholesterol management in the secondary prevention subgroup: about half of the participants in the Tromsø Study V reported to be on LLDs, and 60% of all men and 77% of all women in this treatment-eligible group had TC levels above the recommended target of > 5 mmol/L (paper I). Our findings from three Norwegian counties in 2000–2001 (papers I and III), and a comparative study among participants from the Oslo Health Study,[116] revealed a similar trend.

Cholesterol management with LLDs for secondary prevention is now widely accepted and recommended. The observed gap between reported and recommended use may involve doctors not starting therapy or patients who stop taking their medication (poor compliance).

Although most younger MI patients in Norway now seem to be discharged with a statin, this was the case in only one in ten older individuals (> 80 years).[117] Taking into account prescription data that are missing for individuals living in

institutions, we found a corresponding drop in prevalence of statin use in both genders in this age category (paper IV). In line with this, and as observed in other studies, younger age predicted LLD use for secondary prevention in both men and women,[83,85] [118-120] and LLD users reported having had an MI more recently than non-users (paper I).[118-120] Thus, apart from a reluctance to start LLDs in very old people, individuals having their MI diagnosis prior to the dissemination of the statin trials may be missing out during long-term follow-up in primary care. A Danish, nation-wide, health registry, linkage study of long-term compliance with statins after an acute MI concluded that, unless initiated at the time of discharge from hospital, the likelihood of ever receiving statin treatment was small.[121]

Not only physicians, but also patients influence cholesterol management with LLDs, as a result of, for example, side effects of these drugs. In general, statins are well tolerated, at least at the relatively low dosages commonly used in our population (paper IV).[18,22] Once started, most patients in Norway seem to adhere to treatment for many years[117,122] and also in other countries with comparable reimbursement systems, such as Denmark.[121,123] In the Tromsø Study V (paper I), 917 individuals reported current and 105 previous use of LLDs, so about 10% had stopped their therapy, underlining that adherence to therapy may be less of a problem in Norway with almost full reimbursement for LLDs.

Primary prevention

Paper I identified a large discrepancy between guidelines for LLDs in primary prevention and guidelines for LLDs in clinical practice. Taking into account the presence of coexisting risk conditions, half our study population who had no CHD had a raised TC level, only a minority of whom were on LLD therapy. However, apart

from smoking, the major risk factors (hypertension, diabetes and older age in women) predicted LLD use for primary prevention (paper I).

To target primary prevention intervention, the Norwegian guidelines recommend assessment of baseline risk using the Framingham risk model as a tool in everyday practice.[44,45,54] Thus it can be argued that the 'present situation' of cholesterol management with LLDs for primary prevention is presented incompletely when defined according to the TC level in those with coexisting risk conditions, such as diabetes and/or hypertension in paper I. Taking into account the predictive value of all risk factors included in the Framingham risk model (TC, blood pressure, diabetes, age, gender and smoking status) would reveal a more complete picture of the 'present situation' compared with the recommended level of LLD use.

However, Framingham-based risk assessment of asymptomatic subjects in the OPPHED Health Study (paper III) as well as participants in the Oslo Health Study[116] revealed the same impression of the current situation in Norway. Already at 60 years of age, a third of men reporting no use of LLDs in the primary prevention subgroup had a Framingham 10-year risk score $\geq 20\%$, increasing to about 80% of all men aged 75 (paper III). Corresponding figures in 60- and 75-year-old women were 5% and 10%, respectively. Projection of risk in younger individuals to risk at 60, would probably have increased the proportions eligible for LLDs even further. Obviously, and despite increasing LLD sales, there would seem to be a potential for much higher LLD sales if recommendations for cholesterol management in asymptomatic individuals were to be followed, among men and elderly in particular. Our study highlights the need of an evaluation of actual health care, as well as patient implications of a recommended 'cut-off' for intervention among individuals who are presumed to be healthy.

The Norwegian situation is not unique, however. Although population-based reports on cholesterol management for primary prevention are scarce, a gap has been observed between actual use and the recommended level of use in Dutch and British populations.[86-91] For example, 21% of all English asymptomatic men and women aged 30 and over were eligible according to the Framingham ≥ 20% limit, of whom 8–9% were actually on LLDs.[86]

On the other hand, when intervention thresholds for primary prevention are set according to a certain risk limit, the accuracy of the given risk model would obviously have an impact on the number of individuals assessed as eligible for this intervention. Concerns have been raised about whether the functions of the Framingham risk model can be generalized to other populations – particularly concerns about the overestimation of risk, and proportions eligible for intervention, when applied to western and northern European countries.[58-61] How accurately the Framingham risk model predicts the true baseline risk of having a CHD event in the future, when applied to a Norwegian population, remains unknown, however.

Dosing and choice of statin

Much attention has been focused on the fact that many patients are never offered treatment, whereas dosing has received less attention.

Overall achievement of the TC target among LLD users was suboptimal, with only 40–60% of the statin users achieving the recommended target of 5 mmol/L (papers I and III). This is consistent with results from other studies in Norway during the same period,[116,122] as well as from studies of other European populations.[86,90,124] It also seems to provide a potential for optimizing statin doses. In our study from the NorPD (paper IV), only 20–30% of all simvastatin users were on doses corresponding to the

dose (40 mg) used in pivotal trials, such as the Heart Protection Study.[28] Thus, the majority were on a daily simvastatin dose of 20 mg or less. Furthermore, about half of all atorvastatin users were on a daily dose of 10 mg, which is considered to be equipotent with simvastatin 20 mg. Although the trend in Norway[122] and other European countries reflects a steady increase in dosage over time,[6,125] suboptimal dosing seems to be a general problem.[84,121,126] So, why are LLD users on low doses despite poor achievement of the TC target? For example, more frequent use of a 40 mg daily dose of simvastatin corresponds to TC reductions of above 30%, which would have the potential to bring many patients down to the TC target of 5 mmol/L.

One reason for not titrating LLD doses upwards may be concerns about potential side effects at higher doses. However, findings from the Heart Protection Study, as well as meta-analyses, support the overall safety and tolerability profile of simvastatin up to this dose.[18,22,127] In Norway,[77,122] as well as in other populations, it seems that patients largely remain on their initial doses, and these are seldom adjusted during long-term therapy in primary care.[121] Thus, the reason why patients are maintained on low doses may be a result of inadequate monitoring of these patients, as reflected in the low frequencies of lipid tests and treatment changes after the initiation of LLD therapy, revealed in a study of primary care patients in Norway.[122] In this study, about a third of patients did not have a follow-up lipid test taken during the first 4 months of LLD therapy. A year after the initiation of therapy, 15% had still not had a follow-up lipid test, and most patients (70%) remained on their initial drug and dose, despite the TC goal being achieved in only a third.[122]

In our study from the NorPD (paper IV) only a minority (2–5%) of all statin users were on high-dose therapy with either 80 mg simvastatin or 80 mg atorvastatin.

According to the more recent statin trials, published from 2004 onwards, 'aggressive' lipid reductions with statins for secondary prevention will produce additional clinical benefits to those observed with more moderate statin therapy.[32-35] Hence, the 'previous' recommended LDL-C target of 3 mmol/L has now been lowered in many guidelines. For secondary prevention, the British Hypertension Society now recommend an LDL-C < 2 mmol/L, and American guidelines (NCEP ATP III) recommend an LDL-C < 1.8 mmol/L. However, concerns have been raised about the increase in incidence of adverse effects with higher doses.[37-39] To put maximal statin therapy, such as with 80 mg simvastatin or atorvastatin, on the same footing of clinical confidence as conventional doses, more experience with the use of doses at this level may be needed. Increasing the focus on the benefits of aggressive lipid reductions will, however, most probably cause a continued change towards more frequent use of higher doses in Norway in the future.

In paper IV we found widespread use of atorvastatin, corresponding to the figures in most European countries.[6] June 2005, updated reimbursement regulations were launched in Norway that required prescription of the off-patent drug simvastatin as first choice, in order to reduce cost. [66] One reason for this may be to ensure cholesterol lowering in severe cases, because atorvastatin is more potent at lowering TC levels on a milligram-for-milligram basis than other statins.[13] However, in our study, 80–90% of all atorvastatin users were on a daily dose of 20 mg or less, so it should be possible to switch most of the current atorvastatin users to simvastatin. Obviously the new reimbursement regulations have influenced the choice of statin in Norway. An evaluation of prescription data in the period following the introduction of the regulations and up to February 2006 reported that almost all new users are now started on simvastatin, and 30% of prevalent atorvastatin users had been switched.[128]

5.3.2 Cholesterol management with LLDs – implications for primary prevention through the implementation of recent European guidelines

The implementation of European guidelines, with intervention thresholds based on the SCORE high-risk model, could imply a sixfold increase in the number of Norwegian adults aged 45–79 years on LLDs for primary prevention (paper II). The major contributors to the overall increase in the use of LLDs for primary prevention would be more frequent drug use in men and elderly people. As confirmed in two other Norwegian population-based studies, risk assessment by the SCORE high-risk model may categorize a large proportion of asymptomatic adults as high risk for having a fatal CVD event.[129,130] In line with the Framingham-based intervention thresholds, the implementation of SCORE-based thresholds could have a huge impact on the number of individuals on LLDs for primary prevention. These estimates have provoked a debate about the estimated impact of the guidelines on risk labelling, medicalization and resource allocation in the health-care system.[115,131,132]

Strictly speaking, the target population for CVD risk prediction by the SCORE high-risk model, and thereby for evaluation of treatment eligibility, is those aged 45–64 years.[51] Up to the age of 60 the gap between recommended and current LLD use was seen almost exclusively in men. However, the European guidelines do not discuss an upper age limit for prevention intervention in primary prevention. Furthermore, LLDs are used extensively among elderly people in clinical practice. For this reason, we chose to evaluate treatment eligibility using the SCORE model in individuals aged up to 79. Furthermore, in our study we chose not to project risk in younger people to risk at 60, as recommended by the European guidelines. The actual implications of the European guidelines, as presented, are therefore underestimated, e.g. with

extrapolation of risk a minority of men aged 40 or older would be classified as at low risk.[129,130]

Importantly, there may be factors contributing to an overestimation of the 10-year risk of a fatal CVD event, and thereby to treatment eligibility, through use of the SCORE high-risk model. Trends for CHD incidence and mortality in most industrialized countries are currently declining.[133] Figures from national mortality statistics revealed that the mortality rate from CHD among 45- to 74-year-old men decreased 50–60% in the period 1990–2001.[52] Risk prediction using the high-risk SCORE model, derived from cohorts observed in the years 1974–94, is implicitly prone to overestimation in this situation. Thus, a recent Norwegian study showed that the SCORE high-risk model overestimated the risk of a fatal CVD event in men and elderly women, compared with the 10-year risk estimated from observed mortality rates in the period 1999–2003.[130]

In this situation, our estimated impact of the SCORE-based intervention threshold, suggesting more frequent drug use in men and elderly people in particular (paper II), may at least partly be due to an overestimation of risk in these individuals. Similar overestimation of the SCORE high-risk model is reported in a German population.[134] Moreover, in this study there was moderate agreement between the SCORE high-risk and the version of the Framingham risk model predicting fatal CVD events, when the participants were ordered into risk deciles. The limited accuracy and disagreement between currently available risk assessment models highlight the importance of evaluating risk-scoring models against epidemiological data, taking into account the changing trends in risk factors and cardiovascular death, before implementation in clinical practice in Norway and other countries.

The currently available models predict the risk of having a fatal CVD event (SCORE) or any CHD event (Framingham) in the future. Interestingly, these models with accompanying guideline-defined 'cut-offs' for being at high risk, seems to produce an unequal number of individuals crossing this limit. E.g. 65% of all 55-59 year old men and 85% of all 60-64 year old men were at high risk according to the SCORE based 5% threshold (paper II), as compared to a third of all 60 year old men assessed according to the Framingham based 20% threshold (paper III). Using one or the other recommendation would obviously have an impact on the number of individuals defined as being at high risk, as well as eligible for LLDs, in clinical practice.

5.3.3 General aspects of LLD use that may contribute to regional differences in LLD sales

Higher prevalence of use, with a greater tendency towards use of LLDs in primary prevention, higher PDDs with more LLD users achieving the TC target and extensive use of atorvastatin may be factors that contribute to higher overall LLD consumption (papers III and IV).

Ideally, the geographical variations in prevalence of statin use, as revealed by the NorPD (paper IV), should reflect variations in the size of the population eligible for such therapy. Although similar proportions seemed to be eligible for therapy, there was a greater tendency towards use of LLDs in primary prevention in the high-using area Hedmark (paper III). There is still a gap between current practice and Framingham-based intervention thresholds in all counties studied (paper III). Regional variations in current LLD sales may be small compared with a 'scenario' of full implementation of the guidelines in either region.

Our findings may reflect uncertainty or variations in cholesterol management in asymptomatic individuals (primary prevention). The guideline-defined outcomes for primary prevention may not be feasible, and individual judgements of when to start therapy may result in regional variations in LLD use and thereby in LLD sales. There may be complex barriers to LLD prescribing in primary care, such as concerns about cost, increased workload, medicalization, and difficulties in prioritizing patients and using risk-assessment tools.[135] The observed gap in papers I–III between current practice and guidelines for primary prevention may very well illustrate these practical and ethical barriers to the implementation of current Framingham (as well as SCORE)-based intervention thresholds in clinical practice.

Apart from higher prevalence of use, a systematically higher PDD for all relevant statins in the high-consumption county, Hedmark, influences total level of, and thereby variation in, statin consumption (paper IV). Furthermore, a higher proportion of the statin users in Hedmark achieved nationally recommended cholesterol treatment goals, underlining the tendency of an overall more aggressive cholesterol treatment in the high-consumption county, Hedmark (paper III). The success in achieving the target TC level might, however, be influenced by the use of higher dosages of LLDs or simply by increased continuity of use. Although we do not know to what extent the LLDs dispensed are actually ingested, we found no differences in the number of tablets dispensed per day to indicate that variations in continuity of use were a major contributor to differences in achievement of TC targets among the counties.

Obviously the PDD, and to what extent the PDD deviates from the official DDD, may limit the extent to which the statin sales statistics presented in DDDs reveals a 'true' picture of the trends of prevalence of use. Not surprisingly, the

estimated PDDs for all statins were higher than the DDDs – up to twice the DDD for atorvastatin (paper IV). All statins studied in large placebo-controlled clinical trials, namely pravastatin (40 mg),[24-26,31] simvastatin (20–80 mg),[4,28,33] lovastatin (40 mg),[27] fluvastatin (80 mg)[136] and atorvastatin (10 and 80 mg),[29,32,34,35] have used a statin dose higher than the official DDD. The official DDDs for all statins have remained unchanged since 1994 and have not been adjusted in line with the new clinical documentation published over the last decade.[67] In addition, the discrepancy between DDDs and PDDs may vary between statins (paper IV), e.g. the estimated PDD of atorvastatin (18–22 mg) was twice the official DDD of 10 mg, whereas the PDDs of pravastatin and simvastatin were 1.5–1.6 times the official DDDs. Hence, extensive use of atorvastatin, combined with a systematically higher PDD for all relevant statins in the high-consumption county Hedmark, influences total level of, and thereby variation in, statin sales. Interpretation of the relative increase in LLD sales in Norway over the years, with longstanding regional differences, should take into account the PDDs and the choice of statin.

6. Concluding remarks

The overall sales of LLDs in Norway has increased dramatically since the statins entered the market in the early 1990s. In line with this, within Norway the intercounty variations in LLD sales have been large and persistent. Along with publication of landmark statin trials, national guidelines on cholesterol management that define LLD-eligible individuals have been issued. Traditionally, information on LLD use in the general population in Norway has been limited to figures from whole sales. An evaluation of cholesterol management with LLDs in the total population, however, presupposes information on LLD use and cardiovascular morbidity and risk factors in individuals.

Thus, this thesis contributes the following findings:

- Despite increasing LLD sales, with Norway being one of the 'top-selling' countries in Europe, there is a large gap between current practice of cholesterol management and guidelines.

- There is a potential for increasing the dose of statins to improve the documented suboptimal achievement of the TC goal in about half the current LLD users.

- Adaptation of European SCORE-based intervention thresholds for primary prevention could involve a larger part of the population taking LLDs, particularly among men and elderly people.

- Higher prevalence of use, with a greater tendency towards use of LLDs in primary prevention, higher PDDs with more LLD users achieving the TC target and extensive use of atorvastatin may be factors that contribute to higher overall statin consumption.

- Interpretation of the published increase in whole LLD sales over the years, with national and international differences in consumption, should take into account the differences in the relationship of DDD/PDD and the choice of statin.

7. Practical implications and further perspectives

When intervention thresholds for primary prevention with LLDs are defined according to a certain baseline risk limit, the accuracy of the given risk model would obviously have an impact on the number of individuals assessed as eligible for primary prevention intervention. The limited accuracy and disagreement between currently available risk assessment models highlight the importance of evaluating risk-scoring models against epidemiological data, taking into account the changing trends in risk factors and cardiovascular death, before implementation in clinical practice in Norway.

On the other hand, our study highlights the need for an evaluation of the actual health-care implications of a recommended 'cut-off' for intervention among individuals who are presumed to be healthy. There is a large gap between current and recommended levels of cholesterol management with LLDs for primary prevention, particularly for men and elderly people. Actual adherence to prevailing guidelines would undoubtedly imply a heavy load on the health-care system. If guidelines were to fulfil their intention of being an effective tool in targeting this intervention, this would obviously presuppose taking into account the total resources and follow-up capacity in primary health care. The 'cut-off' for the health-care system prioritizing LLD therapy for primary prevention should be a matter for discussion when revising national guidelines. In addition, feasible thresholds for primary prevention may contribute to less regional variation in LLD sales.

Methods used in former Norwegian studies that evaluate cholesterol management for secondary prevention have included audits of selected primary care clinics, or population-based studies, as included in this thesis. However, they are time-consuming to perform, and therefore often reflect the status of some years ago. The

Norwegian Patient Registry (NPR) was established in 1997, and was established mainly for administrative purposes.[137] The NPR covers almost all inpatient and outpatient hospital care in Norway, including diagnoses, but does not (yet) include a unique person identifier, derived from the Central Population Registry, making it unsuitable for linkage to other health registries. However, presupposing the inclusion of a person identifier in the future, linkage of information from the NPR to the NorPD could provide an effective system for monitoring present treatment status in those with established CVD.

8. Errata

Paper I

Subjects and methods, page 644: the number of participants in Tromsø IV invited to Tromsø V should be 6961 not 7413.

Table 2: Number of men without hypertension are 1576 and not 1676

Table 2: Number of men without diabetes are 3236 and not 3286, percentage of those on LLDs are 12.5 and not 12.9

Paper II

Methods, page 2674: the number of participants in Tromsø IV invited to Tromsø V should be 6961 not 7413.

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Paper I

Paper II

Paper III

Paper IV

Appendix A:

Questionnaires: the Tromsø Study V

Separate questionnaires for subjects < 70 years and subjects > 70 years

Appendix B:

Questionnaires: the OPPHED Health Study

Separate questionnaires for subjects < 70 years and subjects > 70 years