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Power of the Pill

Views about Cardiovascular Risk and the Risk-reducing Effect of Statins

PER LYTSY

ACTA
UNIVERSITATIS
UPSALIENSIS
UPPSALA
2010

ISSN 1651-6206
ISBN 978-91-554-7793-6
urn:nbn:se:uu:diva-121776

Dissertation presented at Uppsala University to be publicly examined in Enghoffsalen, Ingång 50, Akademiska sjukhuset, Uppsala, Friday, May 21, 2010 at 09:15 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in Swedish.

Abstract
Lytsy, P. 2010. Power of the Pill. Views about Cardiovascular Risk and the Risk-reducing Effect of Statins. Acta Universitatis Upsaliensis. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 556. 85 pp. Uppsala. ISBN 978-91-554-7793-6.

Medical treatments with statins are prescribed to patients with increased risk of cardiovascular events. The benefits from statin treatment are well documented in clinical trials, but long-term adherence in patients is low, indicating that patients have an uncertainty about the necessity and benefits of treatment.

The aims of this thesis were to investigate how patients and doctors view different aspects of statin treatment. Further aims were to investigate if the cardiovascular risk level in patients affects their views about different aspects of statin treatment. Yet further aims were to compare health behaviours and views about risk factors in patients using statins to a non-treated population.

Data was obtained from patients (n = 829), doctors (n = 330) and a population sample (n = 720) using postal questionnaires. Views about the effect of statin treatment were assessed in different ways for patients and doctors. Patients based their assessments on their own situation, and doctors' treatment decisions and assessments of anticipated effect of treatment were based on two hypothetical patient cases.

The results indicate that patients greatly overestimate the general effect of statins, compared to efficacy results reported from clinical trials. Patients' previous coronary heart disease or high overall risk were factors not associated with their views and expectations of treatment effect. Statin users with an internally perceived health control and patients satisfied with their doctor's treatment explanation reported higher beliefs in treatment necessity and benefits. Statin users reported having better health behaviours and generally rated risk factors as more important than the non-treated population. Doctors had suboptimal understanding of the number of patients expected to benefit following five years of statin treatment and had a varying understanding of statins' ability to prolong life.

Overall the results illustrate that patients and doctors have different perspectives and views of the benefits from statin treatment which puts emphasis on how statin treatment is discussed in the clinical setting.

Keywords: Statins, lipid-lowering drugs, cholesterol, treatment expectations, beliefs, adherence, health behaviour

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ISSN 1651-6206
ISBN 978-91-554-7793-6
urn:nbn:se:uu:diva-121776 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-121776)

To Birgitta, Lova, Agnes and Ellinor with love.

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List of papers

These papers will be referred to in the text by their Roman numbers.

I. Lytsy P, Burell G, Westerling R. Cardiovascular risk factor assessments and their associations with health behaviours – a comparison of patients using statins with a non-treated population. (submitted)

II. Lytsy P, Westerling R. Patient expectations on lipid-lowering drugs. *Patient Educ Couns* 2007;67(1–2):143–50.

III. Lytsy P, Burell G, Westerling R. Views on treatment necessity, harm and benefits in patients using statins. *Med Decis Making*. [Epub, Dec 11, 2009 doi:10.1177/0272989X09353196]

IV. Lytsy P, Burell G, Westerling R. How do prescribing doctors anticipate the effect of statins? *Journal of Evaluation of Clinical Practice.* In press.

Now according to Dionysius between man and angel there is a difference, that an angel perceives the truth by simple apprehension, whereas man arrives at the perception of a simple truth by a process from several premises.

Thomas Aquinas (1225–1274); Summa Theologica, Volume III.

Contents

Abbreviations

ARR	Absolute Risk Reduction
ARR/1000	Absolute Risk Reduction per 1000 treated
BMQ	Beliefs about Medicine Questionnaire
CHD	Coronary Heart Disease
CVD	Cardiovascular Disease
EBM	Evidence-based Medicine
HBM	Health Belief Model
RCT	Randomised Controlled Trial
RRR	Relative Risk Reduction
SCT	Social Cognitive Theory

Preface

How do you come up with the idea of writing a book that very few people will actually read? Anyone deciding to write a dissertation probably has their own answers to that question. In my own case, I am indebted to one particular patient who I met in my early clinical practice. As a newly examined physician I had sworn to practice medicine in accordance to the Hippocratic ideals: never to intentionally harm a patient but always to try to cure, relieve and comfort them according to my best knowledge. However, what interested me the most was the possibility to help people maintain healthy. Prevention, to avoid unnecessary disease, is arguably the most praiseworthy medical achievement of essential interest of individuals. Put into words by the late epidemiologist Geoffrey Rose: "It's better to be healthy than ill or dead. That is the beginning and end of the only real argument for preventive medicine"(1).

The patient I met, a man a little over 50, was unmistakably in need of a preventive strategy. Being an overweight smoker with poor eating and exercise habits and with a family history of early heart disease, he already had several well-defined characteristics putting him at high risk of premature cardiovascular disease (CVD). His medical examination and blood tests added to the burden, in particular his rather grave hypercholesterolemia. The patient was aware and concerned about his health condition, and I found this a good starting point to try to help him change his situation. We agreed to try to reduce some of his unnecessary high risk factors by changing his lifestyle. I sent a referral to the dietician to go through his eating habits and another one to the physiotherapist to develop a physical exercise program. Furthermore, the patient was determined to stop smoking.

It turned out that these strategies did not work very well. Half a year later he was back in my office with no apparent changes in his risk status and a lower motivation for making the lifestyle changes he no longer believed were achievable.

This man clearly needed to reduce his excess risk, and in concordance with preventive treatment guidelines I suggested that he should consider starting to take a statin, a medical treatment known to reduce the risk of premature heart disease. At first he frowned. Medical treatment? Why? After all he was healthy, he told me, and medical treatments are for the sick and elderly. What the future might bring in terms of disease is uncertain. I

listened to his points, and responded that taking a medical treatment, such as a statin, might push that uncertainty in a more favourable direction, increasing his likelihood to remain healthy. He was quiet for some time, and then asked me to tell him more about the treatment and what he might expect from it in terms of benefits and possible adverse effects. What is the power of the pill, he asked me. I said there was strong evidence that statin treatment reduces the risk of coronary heart disease (CHD) and probably also premature cardiovascular death in people like him. To my best knowledge I also tried to explain the effect, using the different probability figures reported from clinical trials. My patient listened carefully and reflected on my answers, and then asked me for how long he would have to take this medicine. Probably for a long time, I told him.

This patient remained in my thoughts long after he had left my office with a statin prescription in his hand. I had a hard time letting go of his situation and how he responded to the treatment suggestion and the information I gave him. As a physician I was confident that the treatment was right for him. Arguably I had, with some statistical certainty, helped lower his risk of having an unnecessary heart attack, perhaps even saved him from one. Nevertheless, I was not fully content with the situation. It was almost as if I had failed to fulfil my profession's most fundamental principle. Into my office had walked a healthy man. When he left, however, he was arguably sicker than before.

This dissertation scrutinises several of the questions arising from this particular patient. How do patients and doctors understand the risk of CVD? And how do they appreciate the benefits of a solely preventive medication such as statin treatment? Do the contrasting perspectives of patients and physicians match each other, and are there factors associated with any particular views?

These beliefs and different perspectives clash in everyday clinical care when patients meet their doctors. What patients and doctors believe and how they value different actions is not merely of academic interest. Physicians are supposed to base their clinical recommendations on scientific grounds. The understanding of a medical treatment's potential should be based on evidence about its efficacy reported from clinical trials. Therefore, it is important that physicians understand and interpret research evidence of preventive treatments in an accurate way. Furthermore, it is stated that the research evidence should be integrated into clinical practice to improve effectiveness in the treated population. Effectiveness, however, is not the same thing as the efficacy because it also depends on diagnostic accuracy and compliance to guidelines, adherence by the patients and the coverage of health services (2).

Physicians are in a unique position of informing and influencing their patients; in fact, that is part of their job. According to the Swedish health and medical service act (Hälso- och sjukvårdslagen), patients should be informed about their health situation and, if eligible, the potential treatment options to maintain or improve their health (3). Thus, physicians must understand the results of scientific research because this understanding will be passed onto inquisitive patients interested in potential medical interventions.

Patients, by contrast, are supposed to be involved in the decision-making when a new treatment is considered (4). Patients have full right to accept or reject a proposed treatment; consequently, regarding autonomy, patients' rights are utterly clear. However, if patients do not have the correct understanding of the purpose and expected benefits and risks associated with a treatment it undermines their possibilities of making a balanced and justified decision.

All these aspects fit very well into the concept of evidence-based medicine (EBM). EBM is about finding the best research evidence and integrating it into clinical practice with respect to the individual values of patients (5).

Although there are lots of clinical trials assessing the effect of treatments, much less research is performed on how the effects reported from clinical trials are understood and integrated by different groups and how this understanding affects health behaviour. As a research area these questions encompass several different branches of knowledge. To understand the effect of preventive medicines one needs to be acquainted with clinical medicine, biostatistics and clinical epidemiology. Research about how people *view* their health situation and the benefits and risks of treatments rather belongs to the areas of health psychology and health behavioural research. Along with all these areas there is always the ethical perspective: what are the ethical consequences of misunderstandings and deviating goals and perspectives when patients and doctors meet, and what practical handling do they call for?

This dissertation tries to collate all these different perspectives and areas of knowledge with the overall goal of providing knowledge that might improve relevant understanding in the clinical situation.

Introduction

Preventive medicine has enormous potential. For instance, it is estimated that approximately 70% of stroke, 80% of CHD and 90% of type 2 diabetes is potentially avoidable through lifestyle changes (6). These figures suggest that there is a possibility of delaying or even avoiding *premature* occurrences of these disorders. With increasing age the probability of developing most diseases increases, and eventually everyone will die of something. This does, however, not oppose the goal of trying to reduce unnecessary disease burden.

It has been proposed that the goal of public health should include a "compression of morbidity", i.e. an ambition to compress the burden of lifetime illness into a shorter period before the time of death (7). Put in words by the anthropologist Ashley Montagu, the idea is to die young as late as possible. It has been shown that low risk individuals have a greater probability of achieving this goal, (8) making a clear case for adopting preventive strategies.

When societies address potentially avoidable disease they can choose different preventive strategies. As the epidemiologist Geoffrey Rose suggested in his novel and well-cited article *Sick individuals, sick populations* prevention can principally be addressed in two different ways (9). It might either try to reduce the risks and incidences of disease in a population (the population approach) or it could seek to protect especially susceptible individuals in that population (the high risk approach). These different approaches do not necessarily oppose each other, but they do require different thinking and different strategies.

The healthcare system mainly acts through the high risk approach, i.e. it addresses individuals at risk rather than populations. This is in concurrence with Swedish health law, which states that individuals with the greatest need should be prioritised (3). Thus, regarding prevention, the healthcare system should identify and prioritise patients at the highest risk.

Preventive medicine is complicated because it involves several different narratives depending on the different situations and perspectives of health professionals and individual patients. Health professionals, in general, have more medical knowledge, a better understanding of the likely consequences of disease and a better chance of estimating the possibility of preventing ill

health. Patients, by contrast, represent a heterogeneous group with a variety of beliefs of what health is and what should be done to improve or preserve it. However, the most significant difference of perspectives is that patients are subjective to all these matters, whereas healthcare professionals should strive towards objectivity and base their advice on medical facts and consensus.

The initial part of this dissertation will briefly describe the key concepts and areas of relevance to these different perspectives and how they apply to the preventive situation. These concepts include what beliefs and attitudes are, what risk is, how it is perceived by patients and doctors and what we know about their different perspectives. Other important concepts are EBM, which has become an explicit standard that is supposed to guide the behaviour of the prescriber, and adherence, which is about the extent a patient's behaviour corresponds to agreed health recommendations (10).

In this dissertation, CVD will be the “model” disease and treatment with statins will be the “model” treatment. There are several reasons for this. CVDs are by far the leading cause of death in the western world. The aetiology of CVD is multifactorial, and risk interventions are believed to be of high relevance to prevent it. Statin treatment is one of the many medical treatments known to reduce the risk of CVD. Statins are prescribed in both primary and secondary treatment situations. Statins belong to the drug class HMG-CoA reductase inhibitors and are exclusively taken to prevent disease rather than reduce present symptoms. The use of statins has increased since they were introduced in the early 1990s, and today are one of the most frequently prescribed preventive treatments. Therefore it is a suitable model drug when assessing patients' and doctors' expectations of a preventive effect.

Evidence-based medicine

EBM is a concept that encompasses the idea that the best available evidence should be used for medical decisions. It has quickly (the term EBM was first mentioned in a research paper in 1992) (11) become the universal narrative by which research and clinical work is judged.

There are a handful of definitions of EBM, which are all much alike. The Canadian epidemiologist David Sackett has, in a *BMJ* editorial, defined EBM as the integration of best research results with clinical expertise and patient values (5). Yet another frequently cited definition by Sackett is that EBM is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients (12). Thus, EBM forms the decision basis in clinical care. These definitions are also used by the Cochrane Collaboration, an international non-profit organisation that aims to improve healthcare by providing systematic reviews of virtually all fields that involve clinical medicine (13).

The idea of EBM has been remarkably welcomed and quickly adopted by the scientific community. Still there has been some scepticism and objections. Some of the criticism is of relevance to this dissertation, for instance that EBM has mainly been a tool and a standard to evaluate research results, whereas it is neither helpful for improving or evaluating the clinical expertise nor the handling of the casuistic perspective, (14) a perspective that originates from cases in which subjective considerations such as values and goals are of primary interest. This problem has been described as a "gap" between the empirical knowledge and the clinical practice, where the lack of consideration of the values of both patient and health professional is a problem to anyone trying to put EBM into practice (15). The existence of such a gap is further consolidated by the fact that empirical knowledge is not applicable to individual patients, because such knowledge does not answer the principal clinical question: what is best for the patient at hand? (15).

Today there is no real alternative to EBM, although some have argued that EBM has failed to account for other potential warrants for medical decision-making since it does not have a casuistic approach (15). An alternative EBM approach, according to Tonelli, recognises different topics that a clinician must take into consideration. These topics are in line with

current EBM thinking, but they place more emphasis on the importance of patient values and goals as well as the impact of potential system features relevant to decision-making (16).

This dissertation might contribute to a better understanding of the patient perspective as well as other factors of importance for clinical decision-making.

Preventive medicine

Prevention is a series of actions that prevents disease occurrence (17, 18). Preventive actions can target populations or individuals (1, 9). When targeting populations the aim is to remove or shift the distribution of risk factors in the population in a more favourable direction (1, 9). According to Porta's *A Dictionary of Epidemiology,* preventive medicine is defined as the application of preventive measures by clinical practitioners (17).

Prevention is further often described from a thought timeline in the development of disease, defined in the context of levels of prevention. In this timeline, primary prevention is an act that avoids or delays the development of disease before it has become symptomatic, thereby reducing the incidence of disease by personal or communal efforts. The primary preventive approach targets healthy people at risk of developing disease.

Secondary prevention aims at detecting disease early in its development and thereby offering a possibility of further preventing disease development or shortening its duration.

Tertiary prevention is a term used for interventions that aim at reducing the negative consequences of already established disease.

Although these terms are frequently used to describe different situations of prevention, they do not represent clearly defined categories. Neither do they stipulate any specific preventive activities, because the preventive actions are more or less the same regardless of preventive level. The development of chronic diseases, such as CVD, is believed to occur during virtually the whole lifespan. Exactly where the atherosclerotic procedure proceeds from “being at high risk of disease” to established “disease” can be discussed, and it might change as the accuracies of diagnostic procedures are improved.

In the primary preventive situation, the targets of the intervention are people who are healthy. They do not experience any symptoms or negative effects of being at risk of a possible, but not inevitable, future disease. People might be unaware that they have an increased risk that could be reduced. Alternatively they could very well be aware of it, but make a conscious choice to do nothing about it. For this reason healthcare professionals must be perceptive of the patient’s will and values when they decide to evaluate their individual risk and suggest possible medical preventive actions.

Attitudes, beliefs and behaviour

One of the main themes of this dissertation is the exploration and investigation of the respondents' attitudes and beliefs, and thereby there is a need to define these terms. A broad and conceptual definition of the term "attitude" is that it "is a psychological tendency that is expressed by evaluating a particular entity with some degree of favour or disfavour" (19).

According to the Stanford encyclopaedia of philosophy, a "belief" generally refers to an attitude we possess; (20) thus, the terms are used almost as synonyms. In the medical and psychosocial research literature, however, beliefs and attitudes are not used as synonyms, but rather discussed as possible determinants of each other (21, 22).

Dennett has proposed that beliefs could be viewed as a person's inner causes that describe and predict that person's behaviour (i.e. 'taking the intentional stance') (23). To say that a person believes something is then, according to Dennett, another way of saying that that person is likely to behave in a certain way under certain conditions.

The term "view" refers to an individual's personal perception, judgment or interpretation, i.e. an opinion. In this thesis, the term view should be understood to include both attitudes and beliefs.

Measurements of attitudes and beliefs

Beliefs and attitudes are frequently assessed in different academic fields such as the study of politics, economics, sociology and health psychology.
When the measurement of beliefs and attitudes was first formalised in the 1930s it was assumed that accurate assessments would demand large sets of carefully selected questions. Today there are a variety of approaches used, but typically attitudes and beliefs are assessed using single questions with simple phrasings and grading (24). There are several advantages of direct and short assessments of attitudes, for example more complex constructs based on many questions are costly for the examiner and time consuming and demanding for the participants (19). By contrast, longer constructs reduce the risk of random measurement errors, (24) which might be of value when the population sample is small.

When assessing the nature and strengths of beliefs, it has been suggested to ask an appropriate question such as "How strongly do you believe (or expect) that this treatment will help you?" and record the answer using a

visual analogue scale or numerical rating scale with two anchors such as 'not at all' and 'very strongly' (25). Such a scale might have a different grading depending on how refined people's mental representation of the construct is. It has been proposed that "[p]erhaps a 5-point scale is adequate, but perhaps people routinely make more fine-grained distinctions. For example, most people may be able to differentiate feeling slightly favourable, moderately favourable, and extremely favourable towards objects, in which case a 7-point scale would be more desirable than a 5-point scale" (24).

Although assessments of attitudes and beliefs can be tested in terms of reliability, it is not possible to confirm them against factual circumstances. Attitudes and beliefs are subjective notions, which favourably could be further investigated and understood using qualitative research approaches.

Attitudes and beliefs in relation to health

The attitudes and beliefs of patients are of significance in healthcare, where beliefs are recognised as specific predictors of patient behaviour. The beliefs that patients possess about their illness will affect how they cope with their situation (26-28). Thus, understanding a patient's belief about their condition is of relevance for the clinical situation because it offers a possibility to understand their health behaviour and adherence to treatments (29-33). Furthermore, changing patients' illness perceptions, through increasing their knowledge and changing their attitudes, seems to be a way to improve functioning after myocardial infarction (34).

Locus of control is a term that refers to a person's belief about what causes good or bad results in life. The concept of locus of control was first developed by Rotter (35). Within the framework of locus of control it has been shown that having an internal view of control of one's health has many health advantages in areas such as smoking cessation, birth control utilisation, weight loss, information seeking, adherence to medication and sick role behaviours (36). It has also been shown in prospective studies that having an internal view of control is associated with having a reduced risk of common chronic diseases (37). It has been suggested that people having an internal locus of control are more likely to take action and manage their problems, whereas people with an external locus of control have an emotional reaction or avoid facing their problems (38). Wallston et al. developed the multidimensional health locus of control scale, with special focus on health behaviours (39). According to this model, reinforcements for health-related behaviours could be viewed as primarily internal, a matter of chance or under the control of powerful others.

Theories of health behaviours

Health psychology has offered a number of models that seek to describe and understand health behaviour in individuals. Most of these theories are formed to understand how beliefs and attitudes imply lifestyle-related health behaviour. One of the oldest and most influential theories of health behaviour is the health belief model (HBM), which covers several different concepts such as perceived susceptibility, perceived severity, perceived benefits, perceived barriers, cues to action and self-efficacy. How an individual views these main ideas will together form a perceived threat and a perceived cost/benefit analysis that results in a likelihood of action. The model, therefore, suggests that a change in health beliefs will increase the likeliness of a change in behaviour. A persuasive example of this effect was shown in a study where 3432 visitors to a supermarket were screened for cardiovascular risk factors (serum cholesterol, blood pressure, height, weight, level of physical activity and tobacco use). After screening, the participants received a 10-minute brief counselling and interpretation of risk factors. At follow-up, the respondents had increased their knowledge, but also reduced the frequency of consuming high fat food, a finding that was most particular in individuals with higher blood cholesterol levels and high blood pressure and in women (40).

Social learning theory, later recognised as social cognitive theory (SCT), was proposed by Bandura, who suggested that behaviour is a result of the interaction between environmental factors and cognitive processes (41). According to SCT, expectancy, in terms of anticipated value from an intervention, is an important factor that can result in behavioural change. Another component in SCT is how individuals value the short- versus long-term gains following a certain health behaviour compared with not having that behaviour. The third important component in SCT is the concept of self-efficacy, that is the belief that one is capable of performing in a certain manner to attain certain goals.

There are also theories about the relationship between attitudes and health behaviour. The theory of reasoned action/planned behaviour was developed to explain the observed low correlations between attitude and behaviour (42). A basic assumption is that the patient's behavioural intention and their attitude towards health behaviour will determine the occurrence of the behaviour.

Other approaches to understanding health behaviour, such as Leventhal's self-regulatory model, propose that patients' beliefs about their illnesses might guide their action and that an individual's action planning, or coping response, is followed by an appraisal of its effect, which regulates upcoming action planning. Thus, the model is dynamic. Other dynamic health behaviour models suggest there are stages of importance for motivational readiness to change a health behaviour and that the evaluation of a

behaviour's effect on outcome goals determines whether the behaviour change will be maintained or not (43, 44).

Through the years there has been a discussion about how attitudes relate to behaviour, since there are empirical findings suggesting the correlation to be low. According to Ajzen and Fishbein, this predicament was resolved when "it was realised that, although general attitudes are poor predictors of single behaviours, they correlate strongly with multiple-act criteria or behavioural aggregates. In parallel fashion, it was shown that single behaviours can be predicted quite well from compatible measures of attitude, that is, attitude toward the behaviour" (45). Thus, it is understood that beliefs and attitudes towards a behaviour are more accurate predictors of that behaviour than generally assessed attitudes.

When the relationship and predictive ability of attitudes and behaviour were investigated in a large meta-analysis, it was concluded that stronger correlations were found when the attitudes were easy to recall and stable over time. The authors concluded that attitudes more strongly predicted future behaviour when participants had direct experience with the attitude object and reported their attitudes frequently. The strongest correlations between attitudes and behaviour was shown when attitudes were confident and based on behaviour-relevant information (46).

Adherence and non-adherence

Adherence has been defined as "the extent to which a person’s behaviour, taking medication, following a diet and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider" (47). Adherence could further be classified as primary and secondary adherence. Primary adherence refers to a patient's redemption of an initial prescription and secondary medical adherence refers to the correct use of the medication (48). Consequently non-adherence could also be described in terms of being primary and secondary, where primary non-adherence refers to a situation when patients choose not to collect the medications they have been provided in prescription form by their doctor. Secondary non-adherence refers to when patients have collected the drug at a pharmacy, but for different reasons do not take them as intended. Sometimes the term intentional or intelligent non-adherence is used to refer to when patients make reflected and conscious choices not to adhere to treatment (49, 50). Unintentional adherence is assumed to be the result of a passive process less strongly associated with individuals' beliefs and cognitions than intentional non-adherence (51-53).

Compliance and concordance

The term compliance was defined by Haynes in 1979 as "the extent to which a person's behaviour, in terms of taking medications, following diets, or executing lifestyle changes, coincides with the medical or health advice" (54). This definition was previously the most commonly used term, but it has received some criticism because it attributes a greater importance to the doctor in the patient–physician relationship, implying a hierarchy (55).

Yet another term of relevance to adherence and compliance is concordance, which was introduced by the members of the working party of the Royal Pharmaceutical Society of Great Britain (56). Concordance means agreement or harmony and, according to advocators of this term, stands for "the notion that the work of prescriber and patient in the consultation is a negotiation between equals and that therefore the aim is a therapeutic alliance between them" (56). The main idea of concordance is in line in the development of new approaches to understand health behaviour, where patients are regarded as active decision-makers performing a more or less reflected decision to follow treatment recommendations or not (4, 57). However, the term concordance is not without criticism because some regard it as the current politically correct substitute for the term compliance (58). The term is also a description of a patient–physician agreement rather than a behaviour. To the author's understanding there is also a lack of knowledge how concordance between patients and health professionals could be measured, which limits the possibility to operationalise the term for research purposes.

Adherence and clinical practice

Non-adherence (or non-compliance) is recognised as a vast clinical problem, especially in patients with chronic health problems where long-term adherence is believed to be about 50% (47). Long-term adherence to statin treatment seems to be even poorer (59-61). It has been shown outside randomised clinical trials that patients who do adhere to their statin treatment are at a lower risk of myocardial infarction (62-64). Thus, poor adherence to statin treatment is a major clinical problem shown to result in serious and unnecessary cardiovascular events.

Much research has been performed to understand the reasons and predictors of adherence and non-adherence. Empirical research has focused on the role and behaviour of the healthcare provider, the healthcare system and patient behaviour (47). The provider's behaviour includes the information given in the clinical situation. The healthcare system variable includes availability and accessibility of services. The patient perspective has previously focused on investigating associations between adherent

behaviour and patient characteristics, such as age, sex, education, income, marital status, race, religion, psychological traits and so on. Such endeavours have, however, failed to provide any definite or strong associations with adherent behaviour (47, 57, 65, 66).

Ultimately, research about the determinants of adherence aims to develop interventions to improve adherence. According to the results of a systematic review of randomised studies, there is evidence that short-term adherence can be improved by a variety of simple interventions, but improving adherence to treatment of chronic health problems seems to be complex and ineffective (67). The same is true for interventions aiming to increase adherence in patients using statins, and it has been suggested that the patient's perspective and concept of shared decision-making are approaches that might lead to more conclusive answers (68). Such approaches involve different theories regarding people's health behaviours and their beliefs in their medications.

Beliefs about medicines and their relationship with adherence

Patients' beliefs about the positive effect of their medications has been shown to be associated with their willingness to adhere to that medication (10, 56). Horne and Weinman have contributed to this understanding with the development of the necessity-concerns framework (69, 70). This framework is founded on findings that perceived benefits and perceived susceptibility are major themes for forming patients' beliefs about their treatments (29, 71, 72). According to the framework, perceptions of medication can be categorised into beliefs about the necessity of taking medicine and concerns about taking it. It has been suggested that patients carry out an implicit cost/benefit analysis when evaluating a treatment and that the way they balance these aspects will affect their adherence behaviour (49, 70, 73).

The necessity-concerns framework is operationalised through the beliefs about medicine questionnaires (general and specific BMQ) (69) and has been found to predict adherence in several different illness groups such as asthma, (73, 74) renal disease, (75) CHD and cancer (69) and rheumatoid arthritis (76) as well as in patients using multiple chronic medications (77). Other studies, however, have failed to find associations between beliefs and adherent behaviour in conditions such as migraine (78).

Overall, the necessity-concerns framework provides growing evidence that beliefs in medicines are positively associated with adherent behaviour. A recent Swedish dissertation provided further evidence that general beliefs about medicines are associated with adherence (79).

The belief in the positive effect of a medication is arguably of imperative importance when taking preventive treatments such as statin treatment, where the treatment goal is to avoid or delay future disease events rather than relieve present symptoms. Statins work by affecting the blood lipids, and a lowering of the LDL-cholesterol might be perceived as the medication working. An improvement of blood lipids is, however, a surrogate measurement, i.e. a measure that is not directly of practical relevance (18), but believed to correlate to more important outcomes. There is no definite way of telling if a preventive treatment delays or avoids disease events in a specific individual, since neither the occurrence nor the absence of symptoms/events can be interpreted as proof of the effect of a preventive intervention. This means that adherence in the preventive situation largely depends on the patients' expectations and possibly also on the credibility of the advice by the prescribing physician.

The BMQ specific questionnaire does not fully apply to the preventive situation. Some of the 10 items in the questionnaire (items 1, 3 and 5) address how patients view their treatments' influence on current health. This does not match the preventive situation, especially not when treatment has recently been initiated. In addition, the BMQ specific questionnaire does not measure the belief in efficacy. As pointed out by Horne, the belief about necessity is not a form of efficacy belief because it is possible for a patient to perceive a strong need for a treatment, although such a treatment is perceived as only moderately effective. It is conversely possible for a patient to perceive a treatment as highly effective but yet not perceive a personal need for it (80).

Statins

Statins belong to the drug class of HMG-CoA reductase inhibitors, which are used to lower the blood lipids in patients with previous CVD or at risk of developing it. The primary goal of statin treatment is to prevent disease progress and thereby reduce the risk of future cardiovascular events. Hence, the lowering of blood lipids is merely a measure believed to correlate with the primary treatment goal.

The effect of statins

The preventive effect of statins has been investigated in several large randomised trials encompassing different patient populations with varying levels of baseline risk (81-89). Many of these trials have further been investigated in meta-analyses confirming the effect seen in solitary trials (90-94). The newer statins seem to be somewhat more effective at reducing LDL-cholesterol, but in equipotent doses this seems to be of little clinical relevance. Thus, the effect of statins could be regarded as a class effect, meaning that every substance that works thought inhibiting HMG-CoA reductase will exhibit similar effects. The results from effect studies could in short be summarised that statins reduce the risk of CVD in most populations and that the absolute preventive effect increases with higher cardiovascular baseline risk (91, 95). This means that patients with established coronary disease, as well as patients with high overall risk, are more likely to benefit compared with patients with lower risk and no previous history of CHD.

The effect studies of statins include a variety of primary and secondary endpoints which might make the interpretation of the results difficult. In Table 1, one of these endpoints – major coronary event (which in most studies is defined as fatal and non-fatal myocardial) – is listed and summarised out of the results of nine large randomised clinical studies. The effect in the table is expressed in different ways: the relative risk reduction (RRR), the absolute risk reduction (ARR) and the proportion of patients not experiencing a major coronary event during the study period in the treatment group compared with the control group.

The adverse effects of statins are commonly considered manageable and transient with few seriously adverse events, but there is an ongoing debate of the magnitude of adverse effects as well as their potential harm following long-term treatment (96). Statins seem to have beneficial effects in other

medical conditions such as inflammation, dementia (97) and cancer (98). These factors might affect how physicians and patients view the advantages and disadvantages of statin treatment.

Table 1. *Different ways to present the effect of statins on reducing "major coronary events". Data from nine large randomised clinical trials.*

Study	**Mean study period**	**Treatment effect on major coronary event**[b]		**Chance of not experiencing event during study period**		**Preventive setting (primary/ secondary)**
		RRR[a]	ARR[a]	Control group	Treatment group	
4S(81)	5.4 yrs	34%	9.1%	70.5%	79.6%	Sec
WOSCOPS(82)	4.9 yrs	29%	2.5%	90.7%	93.2%	Prim
AFCAPS/TexCAPS(85)	5.2 yrs	37%	4.1%	89.1%	93.2%	Prim
LIPID(84)	6.1 yrs	24%	3.6%	84.1%	87.7%	Sec
CARE(83)	5. 0 yrs	24%	3.0%	86.8%	89.8%	Sec
HPS(86)	5.0 yrs	27%	3.1%	88,2%	91.3%	Prim/Sec
PROSPER(87)	3.2 yrs	19%	2.1%	87.8%	89.9%	Prim/Sec
ALLHAT-LLT(88)	4.8 yrs	9%	1.1%	89.6%	90.7%	Prim
ASCOT-LLA(89)	3.3 yrs	21%	2.0%	90.5%	92.5%	Prim

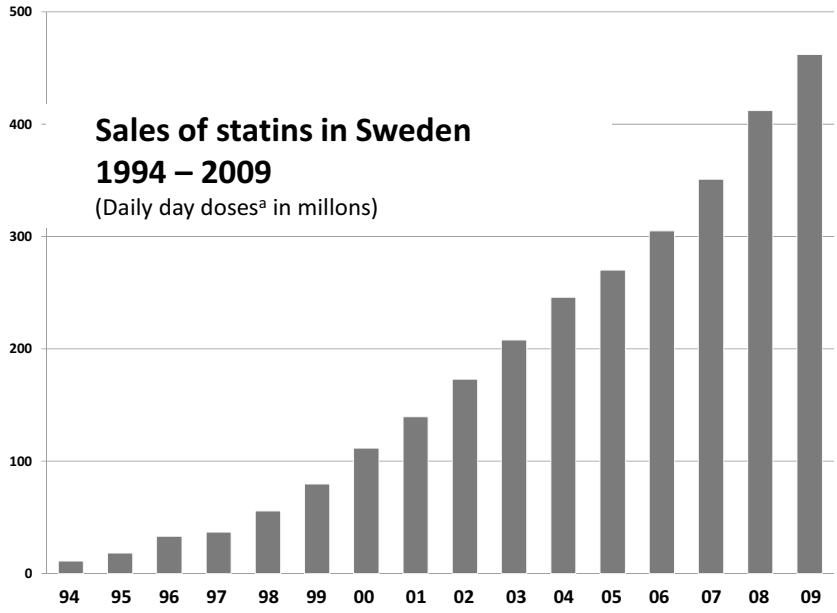
a) RRR= relative risk reduction, (%=percentage), ARR=absolute risk reduction (%=percentage points as in arithmetic difference between study group and control group)

b) "major coronary events" often comprise fatal and non-fatal myocardial infarction, but sometimes also unstable angina or sudden cardiac death.

Statin sales in Sweden

The first statin was introduced in Sweden in the late 1980s, but it was not until in the middle of the 1990s that the positive preventive effect was confirmed in the first clinical trials. The sales of statins have since the mid-1990s increased remarkably (Figure 1). There are probably several reasons for this: intensive marketing activities by the pharmaceutical industry, of course, but also increasing evidence that statin treatment might be of value earlier in life and for increasingly larger populations. The research finding that statins can even affect patients with normal levels of blood lipids has resulted in treatment guidelines with more aggressive treatment target goals, thereby increasing the number of possible patients eligible for treatment (95, 99) .

Figure 1. *Sales of statins in Sweden 1994–2009*



Source: Apoteket statistics

a) Daily day doses were altered for statins in 2009 (see www.whocc.no). For comparative purposes 2009 figures have been adjusted to match data about daily day doses used in earlier records.

Statin use in the population

The steady increase in statin sales has made statins one of the most commonly used medical treatments in Sweden. In 2008, over 760,000 people collected a lipid lowering drug at the pharmacy, which corresponds to an overall use by 8% of the population (100). The usage of statins is much higher in older patients; about one-third of the population between 75 and 84 years are believed to use statins (100).

Cost of statins

For many years the societal costs for statin treatment has increased. In 2003, simvastatin lost its patent, resulting in several generic competitors and a subsequent sharp drop in price. Generic simvastatin is currently recommended as first treatment choice by most of the county council's medical product committees.

The cost for prescription medications for individuals are progressively subsidised in Sweden. This means that the yearly cost for medicines does not exceed 1800 SEK for an individual patient regardless of their usage of prescription medications.

Risk, risk assessment and risk perception

Statins are medications used to lower an individual's risk. In medicine, the term risk is used to describe the probability of an unwanted and unexpected event. A risk factor is a factor that precedes the event and is associated with a higher probability of the occurrence of that event (101). Risk factors can be classified whether they are modifiable or not. A modifiable risk factor can be altered in some way, e.g. losing weight if obese, quitting smoking or treating hypertension. Sex and age are risk factors that are not modifiable. Risk factors can further be classified depending on whether they are causal or not. A causal risk factor directly or indirectly contributes to the increased risk, whereas a non-causal risk factor (sometimes referred to as a risk marker or risk determinant) is merely statistically associated with a higher risk of disease development. If a risk factor is causal and modifiable it might provide a target for intervention. A treatment improving or eradicating a risk factor might decrease the likelihood that the event will occur (102).

Risk estimation involves understanding probability, which is typically derived from statistical calculations of empirical population data. Although each individual in a group contributes to the aggregated statistical characteristics of the group, there is no method to determine how adequate a group measure, such as the average, is to a certain individual (103). Despite this statistical and philosophical dilemma, it is logical for healthcare professionals to estimate risk in individuals and take action to try to lower excess risk simply because, statistically, treated individuals are more likely to benefit than non-treated ones.

Risk assessment

The screening of risk factors is part of every clinical practice, and today’s preventive recommendations for CHD emphasise that high cumulative risk should be treated rather than single risk factors (104-106). An extensive body of clinical and epidemiological research has identified several independent and causal risk factors that are possible to change. For instance, in the INTERHEART, a large case control study, abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial risk factors, low consumption of fruit and vegetables, high alcohol intake and not performing regular physical activity were found to account for approximately 90% of the

population attributable risk of myocardial infarction (107). A recent study has shown that the addition of several more specific biomarkers to conventional risk factors could further improve the prediction of cardiovascular events (108).

Risk assessment through risk motors and assessment aids

Despite the general recognition of several risk factors it is not obvious how to interpret their importance. Most risk factors are, in fact, continuous variables, which means that a cut-off point is needed to discriminate a lower risk from a higher risk. Moreover, when a physician assesses the risk status of an individual it is the combined overall effect of the risk factors that is of importance. The large number of established risk factors, and the virtually infinite number of possible combinations of these risk factors, makes it difficult to assess and predict their combined effect. For this reason several computerised tools, aiming to aid physicians assess and estimate an individual's risk, have been developed (109-111). Such risk motors are based on large follow-ups of health in populations with a focus on known risk factors and their association to incidences of major disease events. Thus, an individual's risk status might be estimated by comparing it to the aggregated data of individuals with a similar health status. The guidelines stressed by the European Society of Cardiology are that the total risk of individuals should be assessed (95). Risk assessment tools, such as the HeartScore (112), are standard in the prediction and management of cardiovascular risk supported by the European Society of Cardiology (95), and are now routinely used in clinical practice. It has been proposed that such risk estimation might be used as a pedagogic tool in the clinical situation to highlight the potential of risk reduction interventions (113). Other authors have pointed out that HeartScore also has some limitations. For example, it can only estimate risk in patients younger than 65 years, it only focuses on the risk of fatal cardiovascular deaths and risk calculations are based on a limited number of risk factors (114).

Risk perception

Although the term risk can be reduced down to a figure that represents the likelihood of a negative health effect, risk perception deals with the appraisal of both the probability and its consequences. Sometimes this is referred to by stating that risk in terms of probability is objective, whereas the perceived appraisal of the consequence is subjective. The latter perspective has been portrayed by the anthropologist Gifford, who deems that having an increased risk status "results in the creation of a new state of being ... that is somewhere between health and disease" (115). Thus, being at an increased risk is moving towards disease and possibly associated with a negatively

affected wellbeing. Furthermore, it has been proposed that the very nature of being at risk implies a demand, a need of action to reduce that risk (103, 116).

Risk perception – how risk is understood and acknowledged by individuals as well as populations– is a research area of its own. According to Rowe, who has provided an important theoretical framework of the concept of risk, risk assessment consists of both risk determination and risk evaluation (117). Risk determination is further constructed of risk identification and risk estimation, where risk estimation includes an assessment of the probability of occurrence as well as the magnitude of its consequences. Risk evaluation is, also according to Rowe, further constructed of both risk aversion and risk acceptance, which together form an individual's idea about whether a certain risk is acceptable or not.

People's understandings and attitudes towards risks are not always rational, nor consistent or coherent. In general, people seem to rate personal risks lower than general (118, 119). It has been shown that when people are faced with probabilistic questions they rely on a limited number of heuristic principles (simple methods to address complex problems), which sometimes leads to systematic errors (120). This means in short that people are not rational when facing risk. Such affect heuristics suggest that judgments about an activity that involves uncertainty are based not only on what people think of that activity, but also how they feel about it (121, 122). The idea that the perception of risk is emotional – risk as feelings (123) – further suggests that when someone feels good about an activity because they regard the benefits from it to be high, they also perceive the accompanied risks associated with it to be low (124).

It is not easy to properly assess people's views on risk since the way the questions are asked might affect the answers. This phenomenon is referred to as "framing". Briefly, framing implies that the way information is presented significantly affects how it is interpreted, and consequently might affect decisions (125-127). There is reason to believe that framing can affect clinical decisions. This is of particular importance in the clinical situation when people are faced with statements that they are at an increased risk and that interventions might improve their chances of maintaining good health. The framing effect is of importance when trying to understand the effect of statins. Several studies have shown that the format of the effect measure, describing the risk-reducing effect, also affects both physicians' and laypersons' willingness to prescribe or take a drug, even though the measurements all originate for the same data (128-133). Naturally, it can be a problem that both doctors and patients do not fully understand the effect measures reported from clinical trials, and the difficulties seem to lie in the understanding of probabilities (134, 135). It has been shown that people in general have poor abilities to understand probabilistic figures, such as

percentages. Gigerenzer reported results from a population survey where 1000 Germans were asked what 40% means. Three possible answers were pre-stated: 40% means: a) one-quarter; b) four out of 10; or c) every 40th person. One-third of respondents did not choose the right answer, which illustrates that innumeracy is a problem (136).

Another quandary, also raised by Gigerenzer, is how a single-event probability should be interpreted by individuals. This is often the case in a preventive situation where a physician might detect an increased risk of a disease. Say, for instance, that a patient's aggregated risk corresponds to an overall risk of dying within the next 10 years according to the estimation of a risk motor. How should that information be interpreted by that individual? One cannot be 15% dead after 10 years. The problem with such a prediction of a single-event probability is that it can never be proved right or wrong and is therefore of limited value to an individual. Therefore, Gigerenzer suggests that to improve risk communication experts need to specify a reference class, i.e. the class of events to which a single-event probability refers. In the example above, that would be the risk of death when certain risk factors are modified. Then, it is possible to compare one risk prediction with another, which would clarify the magnitude of a possible risk reduction. This is the proposed procedure when using HeartScore (105). The same thinking has been further elaborated by Paling, who suggests that a visual aid (Paling's palette) could be used to illustrate the average risk in naturalistic figures with and without treatment to help patient understanding and consideration (137). It has also been suggested that an individual's risk, assessed by a risk table or risk motor, should be compared with the minimal risk of people of the same age and sex (138). This can provide a reference that is meaningful to the prescriber to determine whether treatment is suitable. It would also be of value to individual patients who will then be able to compare their own risk estimate to what is optimal, being the same age and sex.

According to Rowe, the identification of risk is a factor that forms an individual's risk determination. A Swiss study found that citizens knew only about one-third of what was considered "minimal medical knowledge", which included the population's knowledge of typical signs and/or risk factors of four relevant clinical conditions: myocardial infarction, stroke, chronic obstructive pulmonary disease and HIV/AIDS (139). Such results imply that people in general have a limited ability to determine whether they are at an increased medical risk or not.

To summarise, risk perception involves a basic understanding of numbers and probabilities as well as the understanding and appraisal of one's current medical risk and the potential consequences of a disease event. All these factors seem to involve some difficulties when judged by patients. Furthermore, the understanding of risk reduction is framed by how the

efficacy results are presented, and the value of risk reduction is difficult to determine unless there is a good estimate of the baseline (non-treated) risk.

Specific and overall aims of thesis

The aim of this dissertation is to investigate the views on and expectations of risk-reducing statin treatment of patients and prescribing doctors. Further aims are to identify factors associated with different notions about statin treatments and compare respondents' expectations about treatment effect with the effect results reported from clinical trials.

The overall aim is to increase the understanding of how these populations understand and value the advantages and disadvantages of statin treatment.

Paper I

The aim of Paper I is to investigate and compare how a general non-treated population and a statin-treated population assess the importance of known risk factors for CVD. Further aims are to investigate if having a risk factor is associated with how that risk factor is assessed in terms of its importance for the development of CVD, and compare if statin users and non-statin users differ in regards health behaviours.

Paper II

The aim of Paper II is to investigate the expectations of the treatment effect in a statin-treated population. The expected effect will be assessed in two different ways: views about general benefit and subjective benefit. The general effect will be assessed as the number of patients believed to avoid a heart attack during a treatment period of five years. The objective is to provide an assessment in the patient group that can be compared with data from randomised controlled trials (RCTs) evaluating the effect of statins.

The individually expected effect will be assessed as a grading of the likelihood of avoiding a heart attack within three different time perspectives: one, five and 10 years. Further aims are to investigate if sociodemographic factors, medical history of CVD, high concurrent risk of CVD or patient-related factors are associated with any specific notion of treatment expectation.

Paper III

The aim of Paper III is to investigate the different perspectives and expectations of statin treatment regarding its necessity, harm and benefits. Further aims are to investigate if sociodemographic factors, satisfaction with treatment explanation, perceived health control, history of CHD and risk status are associated with certain treatment beliefs. One further aim is to test the strength of the views about whether the necessity, harm and benefits are associated with each other.

Paper IV

The aim of Paper IV is to explore how doctors who commonly prescribe statins (general practitioners, internists and cardiologists) view the need for statin treatment and how they anticipate the effect of treatment based on two hypothetical patient cases. Further aims are to assess if the respondents believe that statin treatment prolongs life, and if so, for how long. Additional aims are to investigate factors associated with the respondents' willingness to prescribe statins.

Participants and methods

Summary of participants and methods

Data were retrieved from three different populations using two different questionnaires. All studies used a cross-sectional approach. The populations, questionnaires, variables and analytic procedures used in each study are summarised in Table 2, and then further described in the text.

Population sample

A total of 1000 people, aged 40–80 years, were obtained from a population sample from the Central Bureau of Statistics. The population sample was contacted in May 2004 using a postal questionnaire. Six questionnaires were returned unopened because the respondent was deceased, had moved without leaving a new address or was in a health situation too deprived to respond to written queries. These six people were excluded. After two written reminders to non-responders, the questionnaire was returned by a total of 720 individuals making the overall response rate 72%.

The statin users in the population sample (n=91, 12.6%) were excluded from the analyses in Paper I in order to obtain heterogeneity in the groups of the population not treated with statins and patients using statins recruited from pharmacies.

The response rate was considered acceptable and similar to that reached using similar procedures and reported from comparable studies.

Table 2. *Summary of the studies' designs, populations, outcome measures and statistical procedures.*

Study	Study design	Study population	Outcome measures	Statistical procedures
I	Cross-sectional	829 statin users and 629 non-statin users	Assessments of risk factors importance. Four health behaviours: • Not smoking • Frequent exercise • Avoiding fatty foods • Eating food with high fibre content	Chi 2-tests. Non-parametric statistics. Multivariate logistic regression.
II	Cross-sectional	829 statin users	Generally expected ARR per 1000 treated (ARR/1000) following five years of treatment. Subjective expected benefit at one-, five- and 10-year perspectives.	Multivariate linear regression. Non-parametric statistics
III	Cross-sectional	829 statin users	Subjective views about the treatment's harmlessness, necessity, ability to prevent disease and ability to prolong life. Dichotomised responses as outcome measures in multivariate analyses.	Chi 2-tests. Non-parametric statistics. Multivariate logistic regression. Cronbach's alpha.
IV	Cross-sectional	330 physicians	Generally expected ARR/1000 following five years of treatment in different preventive settings. Willingness to prescribe statins based on examples. Statins' anticipated effect on life length.	Chi 2-tests. Non-parametric statistics. T-tests and ANOVA. Multivariate logistic regression.

Population of patients using statins

The statin users were recruited in May 2004 after visiting a pharmacy in Uppsala or Gävleborg to have their prescription for a statin prepared. The pharmacies (n=59) had previously received questionnaires in proportion to their prescription turnover. The information given to the pharmacists asked and invited every person visiting the pharmacy to have their statin prescription prepared until all questionnaires were handed out. There were no exclusion criteria other than the statin prescription prerequisite.

Patients received oral and written information about the study by the pharmacist, and patients wishing to participate received a questionnaire to fill in at home. The number of persons declining to participate was registered to control for non-participants. Completed questionnaires were returned anonymously in pre-paid envelopes. No data were obtained or kept by the pharmacists other than a form registering the number of non-responders.

A total of 1195 potential study objects were asked to participate in the study. Of these, 214 declined and 979 questionnaires were handed out. Questionnaires were returned by 829 individuals making the response rate of the distributed questionnaires 84.7% (829/979) and the overall response rate 69.4% (829/1195). All questionnaires included in the analyses were returned within a month of distribution.

The group of statin users consisted of more men than women (54/46%) and their mean age was 64.9 years (SD 9.7). About half of the men (49.7%) and a little over one-quarter of the women (28.4%) reported having a history of CHD, thereby receiving their treatment in a secondary preventive setting.

The population of statin users recruited at the pharmacies was compared to the statin users obtained in the population sample (n=91). There were no apparent differences between the groups regarding age, sex or education. The distribution of the outcome questions used in Papers I–III was similar in the two groups. Thus, the results from the group obtained at the pharmacies were believed to be of relevance to statin users in general. The response rate in the group of statin users obtained at the pharmacies was considered satisfactory.

Population of doctors commonly prescribing statins

Contact information on every cardiologist, internist and general practitioner employed by, or working in agreement with, the counties in Uppsala and Gävleborg were obtained through the county council's records. This procedure was believed to reach almost every practicing physician with the exception of physicians working in occupational health service healthcare and private doctors.

A total of 568 questionnaires were sent out; 63 were excluded because the respondent had quit working there or was unavailable for other reasons. Thus, the total number of possible respondents was 505.

After two reminders, the questionnaires were returned by 333 respondents. Three respondents were excluded because of having other medical specialties than required, making the overall response rate 65.3%. An anonymous one-page feedback form was sent out to non-responders asking them to state their reason for not responding. Approximately half the group of non-responders returned the feedback form. The vast majority stated "lack of time" as their main reason for not responding to the questionnaire. The response rate was believed to be satisfactory, considering the known work load of the respondents.

The study population consisted of more men than women (58/42%). The most common specialty was family medicine (general practitioner, n=208), followed by internal medicine (n=62) and cardiology (n=27). Several doctors (n=40) reported having more than one specialty and 78 doctors were in training to achieve their first specialty. Total work experience ranged from 0–38 years. Mean work experience was 15.5 years for general practitioners, 17.5 years for internists and 14.8 years for cardiologists.

Questionnaires

Questionnaire used in population sample and statin users

The same questionnaires were used to obtain data from the population sample and the stain users recruited from the pharmacies. The questionnaire was developed using queries from previous studies within the department and otherwise. The specific questions assessing the views and beliefs about statin treatment were constructed with the assistance of expertise within the department. Additional viewpoints about the questionnaire were also provided by peers outside the department. The questionnaire was first tested in a pilot study with approximately 30 adults/elderly using a peer-distribution procedure. Questions perceived as unclear or difficult to answer by the respondents were then excluded, adjusted or rephrased.

The questionnaire aimed to collect several variables possibly related to patient views, attitudes and behaviours. The final questionnaire contained 12 pages with a total of 44 questions about health issues, lifestyle, social support and economy as well as questions about the use and expected effect of statins.

Sociodemography

The background questions included questions about sex, age and education. Education was assessed with the question: what is your level of education? Answers were given as compulsory school, secondary school for two years or less, secondary school for two years or more, university or college for three years or less, university or college for three years or more or other education.

Social support was assessed by the question: do you, apart from family, have a close friend with whom you talk to about personal worries? This has been used in previous research (140).

Social participation was assessed with the question how often do you usually meet and spend time with friends or family. Answers were given on a six-graded Likert scale.

Economic strain was assessed as not being able to afford €1500 (14,000 SEK, approximately 60% of the average gross monthly income in 2004) in a week for an unseen need, a question annually used in the Swedish Survey of Living Conditions.

Health

Health was assessed as general self-perceived health, graded on a five-graded Likert scale, which is a question used in the Swedish Survey of Living Conditions. Self-perceived health is a known predictor of disease and mortality (141).

Chronic illness, comorbidity or disability were assessed using a list of 14 common health problems (including diabetes and hypertension). Specific questions assessed if the respondents had experienced one or more heart attacks and if they currently had angina pectoris or if they previously had experienced such an ailment. Patients reporting having had either angina pectoris or one or more heart attacks were considered as having a history of CHD.

Statin use and satisfaction with information

Respondents were asked to state if they take statins. If so, they were asked to mark the brand name from a list of seven brand names. The respondents were further asked to state how they take the medicine in terms of dosage and frequency. These semi-structured questions were seen as simple assessments of primary adherence.

One question asked how their doctor had explained the purpose of the treatment, thereby aiming to assess patient satisfaction with the information received. Replies were given on Likert scales where the replies were phrased as "not at all", "poor", "fair", "good" and "very good".

Views of necessity, harm and benefits from statin treatment

Specific questions were developed to assess the statin users' views about their treatment. One key outcome question in Paper II aimed to assess the views of statins' general ability to reduce the likelihood of a myocardial infarction during the five years of treatment. This question was developed to enable a comparison of beliefs about statins' general effect with the way the general effect is commonly reported in clinical trials.

The question was phrased: imagine that 1000 individuals, with a similar health status as yours, receive the same lipid-lowering treatment as you for five years. How many of these patients do you believe would not suffer a heart attack compared with if they had not have received treatment? Replies were given as a number between 0 and 1000.

The other key outcome questions in Paper II aimed to assess the respondents' subjective views of the anticipated benefit at different time perspectives: one, five and 10 years. Benefits were described as avoiding or delaying a myocardial infarction or angina during the specified treatment time. The questions were phrased: what is the chance that your treatment will be beneficial in terms of preventing a heart attack or angina? a) Within a year?; b) Within 5 years?; or c) Within 10 years? Answers were assessed on seven-graded scales where the lowest number represented ‘‘not likely’’ and the highest number ‘‘very likely’’ regarding the possible beneficial effect.

The key outcome questions analysed in Paper III aimed to assess patients' general views on the health benefits, necessity of treatment and possible harm associated with statin treatment. These questions were phrased as: what are your views on blood lipid-lowering medication on the following issues? Mark the number representing your view.

Treatment…
…reduces the risk of disease.
…is necessary.
…is harmless.
…prolongs life.

A seven-graded scale was used to assess the subject's view on the above topics where the lowest number represented “do not agree” and the highest number “agree fully” with the beneficial effect. The scale was not phrased by words other than described.

The development of the questions assessing a patient's subjective view of treatment was influenced by the understanding that perceived benefits and perceived susceptibility are major themes forming patient's beliefs about treatment (29, 70-72, 142-144). The questions assessing a patient's subjective view were developed to scrutinise these themes. The questions

assessing perceived benefits at different time perspectives aimed to assess an individual's beliefs about treatment efficacy, which is not the same as treatment necessity (80).

The outcome questions were investigated in regards to how they related to each other. All outcome questions assessing beliefs about treatment efficacy and views of treatment necessity, harmlessness and treatment benefits were significantly correlated ($p<0.001$) with each other. There were high correlations among the beliefs in effect at different time perspectives (rho=0.51–0.83) as well as among the views about treatment necessity, harmlessness, statins' ability to reduce the risk of disease and ability to prolong life (rho=0.40–0.67). A correlation matrix among the outcome questions is illustrated in Table 3.

Table 3. *Correlation coefficient matrix between the outcome questions assessing different perspectives of statin treatment. All correlations are significant at the p<0.001 level.*

	a)	b)	c)	d)	e)	f)	g)
a) Benefit* in one year	1						
b) Benefit* in five years	0.83	1					
c) Benefit* in 10 years	0.51	0.81	1				
d) Statins are necessary	0.26	0.31	0.22	1			
e) Statins are harmless	0.14	0.18	0.18	0.40	1		
f) Statins reduce the risk of disease	0.34	0.39	0.34	0.61	0.43	1	
g) Statins prolong life	0.29	0.38	0.34	0.63	0.53	0.67	1

Statistical test: Spearman's rank correlations, two-sided tests.

* Benefit was described as avoiding or delaying a myocardial infarction or angina during the specified treatment time.

Views about risk factors

The respondents were asked to rate the importance of a list of potential risk factors for the development of CVD in people in general. The list of risk factors included obesity, hypertension, alcohol misuse, poor exercise habits, elevated blood lipids, tobacco use, diabetes and poor eating habits. The ratings of the importance of these risk factors were assessed on seven-graded scales, where the lowest number rated the risk factors “not important” and the highest number rated the risk factors “very important” in developing CVD.

Perceived health control

Patients' perceived control of health was assessed with the question: what applies most to you? My health is mostly dependent on: (a) things I do control; (b) things I do not control; or (c) equally by things I do and do not control. This question was an attempt to, in one single question, capture the essence of the concept of locus of control, first developed by Rotter (35).

Health behaviours

Physical activity was assessed with the question: do you perform any regular physical activity in your daily life? (Daily, a few times per week, a few times per month, never or almost never).

Dietary habits were assessed with two questions: are you concerned to try to avoid fatty foods (no not at all, yes to some degree, yes to a high degree) and are you concerned to try to eat foods with a high fibre content, such as wholegrain bread, muesli or root vegetables (No not at all, yes to some degree, yes to a high degree).

Alcohol consumption was assessed using the first three questions in AUDIT (145).

Anthropometric measures on length and weight were used to calculate body mass index (BMI), where a BMI ≥ 30 was considered obese.

Questionnaire used in the population of doctors

The questionnaire used to assess the views of prescribing doctors was developed with the assistance of expertise in family medicine and cardiology. The questionnaire was then critically evaluated by several clinicians and members of the medical product committees in Uppsala and Gävleborg, before it was adjusted and finalised.

The questionnaire contained questions about the respondent's sex, medical specialty(ies), years of experience in that specialty(ies) and primary workplace (primary or secondary care).

The respondents were asked to give their opinion on statin treatment based on two hypothetical patient cases. Patient case I was described as a 52-year-old male with several risk factors, including hypercholesterolemia (total cholesterol 7.3 mmol/L = 285 mg/dL), but without a history of symptomatic CHD. Patient case II was presented as a 69-year-old woman with a history of myocardial infarction, hypertension, type 2 diabetes and with an untreated moderate hypercholesterolemia (6.5 mmol/L = 254 mg/dL).

Patient case I (primary preventive case) was chosen to correspond to an overall mortality risk of 10% within the next 10 years according to the risk motor SCORE (Systematic Coronary Risk Evaluation) (109).

Patient case II was chosen to correspond to an overall mortality risk of 10% within the next five years according the risk motor RiskScore (146). Both patient cases were chosen to correspond to a substantial overall risk, making the eligible for treatment with statins according to the current treatment guidelines (95).

The respondents were asked to consider if they would prescribe a statin based on each patient case and, if so, what substance and dose would they use. The respondents were further asked to assess the expected benefit in a treated population, comprised of patients similar to the hypothetical cases.

The question, for each patient case, was phrased as follows: imagine that 1000 patients, with a similar health situation as the described patient, are treated with a statin for five years. How many of these patients do you think would avoid a myocardial infarction or other ischemic heart disease during this time period, as a consequence of statin treatment? Replies were given in written form as a number ranging from 0 to 1000, which corresponds to the ARR per 1000 treated (ARR/1000).

The respondents were further asked if they believed that statin treatment would prolong life in a patient group similar to the patient cases. If so, they were asked to estimate the average expected life gain, in years and/or months, as a result of treatment.

Variables and analytic procedures

Paper I

In Paper I, ratings of the importance of cardiovascular risk factors were used as outcome variables in univariate analyses comparing statin users and persons not using statins. Furthermore, differences in the ratings of risk factor importance were sought by dichotomised risk status in both statin users and persons not using statins. The distribution of the outcome data was not normally distributed, thereby non-parametric statistical methods were used (Mann–Whitney) to detect differences.

Four health behaviours were used as outcome questions comparing statin users and persons not using statins. In the multivariate analyses, statin users and non-statin users were compared in the same analyses to search for differences associated with their health behaviours. The investigated health behaviours were dichotomised to enable logistic regression.

Exercise was dichotomised as performing exercise daily or almost daily (n=416, 27.4%) compared with not doing so (n=1104, 72.6%). Smoking was dichotomised as being a current non-smoker (n=1280, 83.4%) compared

with current smoking (n=254, 16.6%). Consumption of dietary fat was coded as being very concerned about avoiding fatty foods (n=307, 19.8%) compared with not (n=1231, 79.5%). Consumption of fibres was dichotomised as being very concerned to eat foods with a high fibre content (n=455, 29.5%) compared with not (n=1086, 70.5%).

The fully adjusted models included sociodemographic variables as well as risk factors, comorbidity, statin use and an assessment of the importance of the risk factors.

Paper II

Paper II analysed patients' perceptions of the general effect of statins as well as the individually expected effect rated at three different time perspectives: one, five and 10 years.

One specific objective was to determine if a patient's risk status was associated with their assessment of these outcome questions. For this reason a risk score was created based on the presence of hypertension, diabetes, obesity, no or low exercise and smoking or not in the respondents. All study objects ranged from having none to all five of these risk factors. The risk score was compared with a score created from the sum of the odds ratios of risk factors in the INTERHEART study (107). The comparison of the two scores showed a high correlation (r=0.986, $p<0.001$), thereby the created score used in the analysis was considered clinically relevant. Testing was performed by comparing respondents with a low risk (0 risk factor score), intermediate risk (1–2 risk factor score) or high risk (3–5 risk factor score).

Multivariate linear regressions were used to search for associations between the ARR/1000 assessment and the respondent's age, sex, education, economic factors, social support, social participation, previous CHD, BMI, alcohol use, smoking, choosing food for health reasons and physical activity.

Patients' views about the expected effect of three time perspectives were investigated in univariate analyses using non-parametric statistics (Mann–Whitney and Kruskal–Wallis tests). Associations were sought based on respondents' histories of angina and/or heart attack as well as risk categorisation. Differences were also sought on the basis of respondents' self-rated health, satisfaction about treatment explanation, perceived health control and social support.

Paper III

The key outcome questions in Paper III aimed to assess patients' views on health benefits, the necessity of treatment and the possible harm associated with statin treatment.

The outcome questions were investigated for differences by sociodemographic factors, perceived health control, explanation of treatment and previous CHD and risk categorisation (described above). Differences were sought in univariate models using non-parametric statistics (Mann–

Whitney and Kruskal–Wallis tests) and in multivariate logistic regression models. In the latter analysis, a cut-off point between 4 and 5 was chosen for the questions on disease prevention, life prolongation and the necessity of treatment to establish a comparison of patients who mainly agreed on the statements (53.8–84.0%) compared with disagreeing (16.0–46.2%). The cut-off points were supported by the distribution of the data. A lowering of the cut-off points would create unsatisfactory size differences between the compared groups. An increase of the cut-off point by one step did not affect the main results in any important way. To test the associations among these questions, correlations analysis, reliability tests and factor analysis were performed.

Paper IV

In Paper IV, the respondents based their assessments on two hypothetical patient cases. Based on these cases they stated if they would prescribe a statin, what effect they expected expressed as ARR/1000 and the effect on gain in life length.

To enable comparative analyses the assessed ARR was, for each patient case, categorised into three groups: low, intermediate and high. In the primary preventive situation, replies <10/1000 were categorised as low, 10–40/1000 as intermediate and >40/1000 as high. In the secondary preventive situation, replies <20/1000 were categorised as low, 20–80/1000 as intermediate and >80/1000 as high. The rationale for the categorisation was to create groups of risk assessments that were clearly lower, higher or within the range of effect reported in previous large meta-analyses (90-94).

Differences on the assessment of ARR/1000 were sought in univariate analyses (χ^2 tests and non-parametric analyses) as well as in multivariate logistic regression models. In the regression models, having a "low" or "high" ARR assessment was compared with the "intermediate" group. The respondents' sex, specialty and total work experience were used as independent variables.

The respondents' willingness to prescribe a statin was investigated in univariate analyses as well as in a multivariate logistic regression model. In this model, sex, specialty, work experience, ARR assessment and the assessment of gain in life length were included as independent variables.

The respondents' assessment of a statin's ability to prolong life was assessed in univariate analyses by the respondents sex, medical specialty and workplace using non-parametric statistical methods.

Statistical program

The analyses were performed with SPSS (Statistical Package for the Social Science)/PASW (Predictive Analytics SoftWare) Statistics, versions 14.01–18.0 for Windows.

Summary of methodological approach

The four papers in this dissertation investigate the views about the risk and risk reductions through statin use in three different populations: a population-based sample, in patients using statins and in doctors commonly prescribing statins. A broad set of variables have been collected to search for associations in univariate analyses, and if adequate, included as independent variables in multivariate approaches.

The aim has been to, if possible, investigate the study populations' views in different ways. In terms of the effect of treatment, patients have answered questions about what they believe the effect of statins to be in *general*, i.e. what effect could be expected when a group of patients are treated. The aim has been to ask questions that make it possible to compare the answers with clinically derived effect data. The same approach was used when assessing the expected effects by prescribing doctors.

Furthermore, patients have been asked to assess different views about statins from their subjective perspectives. To such comparisons there are no 'objective' or 'true' responses, thereby the data aimed to search for associations and subgroup differences. This is also true for some of the questions addressed to the physicians, for example statins' effects on life length.

Finally, the views about risk and anticipated treatment effect have then been investigated in relation to behaviour to try to find out how statin use and views of risk factors are associated with favourable health behaviours. The corresponding approach for prescribers has been to investigate how different factors, including the prescribers' views about the effect of statins, affect their willingness to prescribe the drug.

Results

Results Paper I

Statin users had, compared with non-statin users, a tendency to rate several risk factors (elevated blood lipids, smoking, poor exercise habits and poor eating habits) as more important contributors to CVD.

Statin users and non-statin users who reported having poor exercise habits rated 'poor exercise habits' as a less important risk factor than did their counterparts with better exercise habits. The same was true for eating habits. Statin users and non-statin users reporting having poor eating habits rated 'poor eating habits' as a less important risk factor for the development of CVD.

When health behaviour was assessed for the total group, women reported being more frequent exercisers and were more particular about avoiding fatty foods and choosing foods with a high fibre content. By contrast, women were more frequent smokers. Statin users, compared with non-statin users, reported better eating habits assessed as avoiding fatty foods and choosing foods with high fibre content. These findings remained significant in the multivariate analyses adjusting for age, education and medical conditions.

The overall results suggest that statin users are more aware about risk factors and have adopted a better lifestyle in terms of eating habits compared with persons not using statins.

Results Paper II

The average number of patients expected to benefit from the treatment during a five-year treatment period (general effect) was believed to be 531 out of 1000 (53.1%). Patients with university level education had a significantly lower expectation compared to patients with other education (45.7% vs. 54.7%, $p<0.01$), but this effect was weakened in a linear regression model adjusting for other factors.

Patients had, in general, a positive expectation of their own treatment. A history of CHD was not associated with any particular notion on treatment expectation at any time perspective. A comparison of the three risk groups revealed that patients with the highest risk presented a slightly *more negative*

view about expectation of effect at the 10-year perspective. Apart from that there were no significant findings according to the risk stratification.

Satisfaction with the physician's treatment explanation was significantly associated with a higher treatment expectation at all time levels ($p<0.01$ at all time perspectives). Patients with a good global self-rated health had a significantly higher expectation about treatment at the one-year perspective compared with patients with a lower self-rated health, ($p=0.043$), but this finding did not reach statistical significance at the other time perspectives.

Patients' perceived control of health was significantly associated with treatment expectation at all time perspectives where a patient reporting being in control of their health presented a considerably more positive view on benefiting from their treatment.

Patients reporting having no close friend other than family were significantly associated with a more negative expectation on treatment benefit at the 10-year perspective. None of the following revealed any impact on the expected treatment effect at any time perspective: sex, level of education, participation in social activities, obesity, history of smoking, alcohol usage or health concern when choosing food.

The overall results in Paper II suggest that patients using statins overestimate the treatment's expected general and absolute effect. Furthermore, a patient's overall risk status and previous CHD do not seem to be factors affecting patients' beliefs about treatment effect, which contrasts with the medical rationality applied by clinicians when determining if treatment is warranted. Factors relating to the patient–physician relationship and the patients' perceived control of health seem to be associated with patients' beliefs about treatment effect.

Results Paper III

One of the main results in Paper III was that neither risk status nor a history of angina and/or myocardial infarction was associated with patient views on treatment benefits, measured as statins' ability to reduce disease risk or prolong life. Apart from risk level and medical status, patient views on statin treatment were examined by sociodemographic, socioeconomic and personal characteristic variables. In these analyses, women agreed more than men that statins are necessary. Older age groups agreed more that statins are harmless and less that statins prevent disease events.

A higher education was associated with a lower agreement that statins are necessary and that statins prolong life compared with patients with a lower education. Internally perceived health control was associated with a more optimistic view on all occasions, but did not reach statistical significance for

the question on harmlessness. Patients' satisfaction with the explanation of the purpose of the treatment was significantly associated with a more favourable view on all four outcome questions. None of the outcome questions were significantly associated with economic strain, social participation, alcohol use, exercise habits, current smoking, obesity or self-rated health.

The findings in univariate analyses were analysed in multiple logistic regression models. In the fully adjusted models, a lower than university level education was associated with a more favourable view that statins are necessary and that the treatment prolongs life. Having internal perceived health control was associated with a more optimistic view on statins' ability to prevent disease events and prolong life. Patients reporting satisfaction with the treatment explanation presented a more favourable view on all the outcome questions. Patients with a high risk according to the risk index had a higher perception that statins are necessary, but did not present any favourable views on treatment benefits.

Correlation analyses among the key outcome questions resulted in highly significant correlation coefficients (r=0.337–0.6.35, $p<0.001$). Factor analysis performed on all four outcome questions revealed a high level of consistency with factor loadings ranging from 0.67 to 0.86 and with a Cronbach's alpha of 0.77, thereby presenting a high level of internal reliability.

The overall results in Paper III imply that cardiovascular risk level and previous CHD are not factors that are associated with how patients value the potential benefits from statin treatment. Furthermore, patients' views about the necessity, harmlessness and treatment benefits do not seem to be independent dimensions of patient belief. Rather the results suggest that patients perceive statins with one overall heuristic approach: is statin treatment good for me?

Results Paper IV

Paper IV explored the views about statin treatment among doctors commonly prescribing this medication. There was a variety of responses among physicians about the anticipated ARR/1000. The average assessed ARR/1000 was 52 in patient case I and 63 in patient case II. As a result of positively skewed data, the median was markedly lower: 20 in both patient cases. When the assessed ARR/1000 was compared with the categorisation of the results from large meta-analyses of treatment effect, several doctors had an inappropriately low or high ARR assessment. Only 30.9% of assessments in patient case I and 35.7% in patient case II were in the

intermediate interval, best corresponding to evidence-based results. Even if the cut-offs of low and high assessments were adjusted to be more tolerant of assessment close to data supported by evidence many doctors were still far from a feasible expectation.

In the multiple logistic regression, being a female doctor was associated roughly with a twofold probability of making a high compared with an intermediate ARR assessment. This was true for both the primary and secondary preventive cases. Being a general practitioner or training to acquire their first specialty was associated with making a low compared with an intermediate ARR assessment in the primary preventive patient case.

The mean expected gain in life expectancy was 3.4 years in the primary preventive situation and 3.1 years in the secondary preventive situation. The distribution of responses was, however, skewed, making the median assessments lower: 2.0 years in patient case I and 3.0 years in patient case II. There was a considerable variation in expectations about statins' ability to prolong life. In the lowest quartile of assessments in the primary preventive situation, the average gain in life expectancy was believed to be 0.1 years compared with an average of 7.1 years in the highest quartile. The corresponding figures, for the secondary preventive case, were 0.5 years for the lowest quartile compared with 6.4 years for the highest.

Based on the two hypothetical patient cases, 89.9% of the respondents would prescribe a statin to patients like the one in patient case I. The corresponding figure for patient case II was 93.0%.

Work position was not associated with a willingness to prescribe statins. Being male was associated with a higher willingness to prescribe statins in the secondary preventive situation. Having a more positive expectation on statins' ability to prolong life was associated significantly with a higher willingness to prescribe statins in both the primary preventive situation (OR 2.27, $p<0.01$) and the secondary preventive situation (OR 6.69, $p<0.01$).

The overall results in Paper IV indicate that prescribing doctors have a varying and suboptimal understanding of the expected effects from statin treatment. The prescribers' beliefs about statins' ability to prolong life seem to be an important predictor of their willingness to prescribe the drug.

Discussion

Paper I's primary aim was to investigate and compare views about risk factors and behaviours in statin users and persons not using statins. Statin users had, compared with persons not using statins, better health behaviours. This finding was most apparent for eating habits, assessed as avoiding fatty foods and eating foods with a high fibre content.

Furthermore, there were consistent findings that statin users tended to rate behavioural risk factors, such as poor exercise habits and poor eating habits, as more important contributors for the development of CVD than did their non-treated counterparts. Although the statin users were somewhat older and had more medical conditions than the non-treated population sample, they also could be expected to have come upon more information from healthcare professionals. Thus, they have had more occasions and reasons to reflect about their health situation. The finding is in line with previous study results showing that individuals under treatment perceive their CVD risk to be higher than non-treated individuals (147).

There are studies showing that a simple screening of cardiovascular risk factors followed by brief counselling might alter beliefs and dietary behaviours (40). But, there is also one study showing that just being screened and not receiving treatment for hypercholesterolemia does not alter health beliefs (148). Perhaps initiating and adhering to treatment will stimulate both changes of the perceptions of risk as well as changes in health behaviours.

There is previous evidence that intensive lifestyle interventions (including diet, exercise, stress management and group support) are associated with changes in psychological distress and hostility (149). Patients adhering to these changes also reported a stronger sense of coherence and perceived greater social support through follow-ups. There is also evidence that lifestyle changes, such as participating in a cholesterol-lowering program, are associated with not only changes in dietary habits but also with reductions in depression and aggressive hostility as well as with lowered plasma cholesterol levels (150). Furthermore, it has been shown that adhering to intensive lifestyle changes is associated with the regression of coronary atherosclerosis compared with people not adhering to lifestyle changes (151).

Together these findings support the idea that lifestyle changes and adhering to treatment are associated with several different improvements of relevance for subjective well being and important health outcomes. These views, beliefs and behaviours might cross-fertilise each other, supporting the idea that multiple health behaviours should be targeted in the prevention of CHD.

The aims in Papers II and III were to assess the views and expectations of statin treatment in a treated population. These perspectives have been advocated as important to understanding the low adherence rate among statin-treated patients (68, 152, 153). One of the principal and consistent results in Papers II and III was that previous CHD or a high risk of such diseases did not affect the patients' views on and expectations of statin treatment. This was an unexpected finding since it is well documented that risk and previous CHD are important factors when determining whether a patient is eligible for treatment or not. There are several possible reasons why previous CHD or a high risk of CHD does not affect patient views. One is that patients do not understand that the absolute likelihood of benefit increases with increased risk. This applies to the work of Slovic and Loewenstein, who have shown that patients use affect heuristics, i.e. do not make deliberative decisions but rather apply a 'rule of thumb' when assessing risk (122, 123). According to the results in Papers II and III, this seems to also be true when patients assess the benefits and risks associated with statin treatment. These results suggest that statistical reasoning and efficacy evidence from clinical trials are of less importance in the clinical situation, and that physicians should appraise their patient's heuristic understanding of their treatments, i.e. their intuitive perception. Thus, enhancing patients' commonsense understanding of their treatment and supporting their beliefs about the importance of favourable health behaviours might offer a strategy to optimise patient involvement, treatment adherence and behavioural change.

Satisfaction with treatment explanation was found among the variables that were highly associated with more optimistic views on benefits, necessity and potential concerns of treatment. This is in agreement with other studies emphasising the importance of the clinical meeting and the physician–patient working alliance (154, 155). It seems logical that patients who feel they are well informed also have a higher agreement that treatment is beneficial.

Another consistent finding was that having a mainly internal perception of health control was a factor associated with a more favourable view of statin treatment. An internal perception of control refers to a patient's belief about what influences their health. Having an internal view of one's ability to control life is a factor that in prospective studies has been shown to be associated with better health outcomes (37, 156). The reasons for the effect

of an internal health locus of control are not fully understood, but it is hypothesised that this helps work towards a positive health-related behaviour (37, 38). In the setting of preventive cardiology, this would include adjusting and adhering to a healthy lifestyle as well as accepting drug treatment as a method of obtaining or preserving health. It has previously been shown that positive health behaviour, such as approving screening procedures or vaccinations, is associated with a favourable adherence to treatment (157).

Most sociodemographic factors were not associated with any certain notion about statin treatment's necessity, harmlessness or benefits or but some were found to be relevant with regard to treatment beliefs. A higher education was significantly associated with a lower (more realistic) view on the general effect of statins. A higher education was also associated with a poorer agreement that statins prolong life and that the treatment is necessary. Consequently, patients with a lower education had a more favourable view of these issues. However, education was not associated with the rating of *subjective* benefits at different time perspectives, suggesting that subjective views about treatment belief are not primarily moderated by knowledge or education. Older age was found to be associated with a higher agreement that treatment is harmless. One possible explanation is that older people, in general, are exposed to more medical problems and are therefore more likely to accept medical treatments as justifiable and perhaps inevitable.

One of the aims of Paper III was to investigate whether beliefs about benefits and concerns are different dimensions in what has been described as an implicit cost/benefit analysis (70). There was a high correlation among the questions on benefit (disease prevention and life prolongation) and concern about adverse effects (harmlessness and necessity of treatment) in Paper III. The reliability analysis performed resulted in an overall Cronbach's alpha of 0.77; thus, the results do not support the hypothesis that benefits and concerns represent different aspects. Instead, patients in this material seem to address themselves with one overall heuristic question: is statin treatment good for me?

Papers II and III did not directly address treatment belief in relation to adherence or time of treatment. However, the respondents were selected when receiving their medication at a pharmacy, which in itself could be seen as an act of primary adherence. The respondents were also asked to state if they took statins and in what way (dose and interval), suggesting that the informants were also secondary adherent. Thus, the studied group is believed to be a selection of patients with better adherence than the total group of patients that receives a statin prescription from their doctor. There are also several other studies that show that belief in the medication is associated with adherence (70, 77, 154, 158, 159). Some studies suggest that adherence

to statins is associated with other positive health behaviours, such as screening tests and vaccinations (157) and that adherence increases when the credibility of the provider is good (154). Poor adherence in the primary preventive setting has been associated with the perception of risk, toxic effects, expected treatment duration,(160) as well as the perceptions that treatment is of limited value (154).

In Paper II, one outcome question was aimed at assessing patients' expectations on the effect of statins in general. Patients were asked to assess the number out of 1000 treated patients (with a health situation similar as the respondents) that would avoid a heart attack during five years of treatment. That question might be perceived as complex, because a rational guess requires an estimate of how many people out of 1000 will suffer a heart attack *without* treatment. On average, the respondents believed that 531 out of 1000 people treated would avoid a heart attack during five years of treatment. This is about 10–20-fold higher than the ARR seen in clinical trials.(81-85) The question assessing the ARR/1000 treated might be disputed for being difficult or abstract for individual patients. Nevertheless, when the same question was used in a subsequent study of 414 statin users, the results were virtually the same (161): mean assessment was 548 and the distribution of answers was similar, thereby indicating a high reliability.

The overestimation of treatment effect implies that there is a large gap between patients' expectations of a treatment effect and the evidence-based effect data of treatment. That such a expectation gap exists is supported by a previous Swedish study examining expected benefits from treatment for hypertension (162). Another study examined the threshold below which a patient is not prepared to take a hypothetical cholesterol-lowering drug. In this study, three different groups were compared: patients just discharged from a cardio unit, patients taking other cardio preventive drugs in a primary preventive setting and patients not taking cardio preventive drugs and without a CVD history. The median values for the threshold of benefit below which the subject would not take the preventive drug were 20%, 20% and 30% ARR for the three groups respectively, which is also far beyond what is seen in RCTs (163).

The gap between patient expectation and actual effect is indeed a dilemma. Patients have a difficulty understanding probabilistic numbers (135), yet in shared decision-making they should be informed about a treatment's anticipated effect (4). However, since patients seem to perceive the ARR of statin treatment as far greater than that found in clinical trials, they are at risk of being disappointed when informed about the efficacy results from RCTs. This is believed to affect their willingness to accept and adhere to treatment (164). There are no obvious solutions to this problem, but the dilemma needs to be further debated.

The difficulties for patients understanding treatment effect are related to understanding the concept of probability (134-136, 165). Unfortunately, the effect measures reported from clinical trials are commonly reported as probability measures, such as RRRs or ARRs or numbers needed to treat. These ways of determining and presenting effects apply to the situation of physicians and policymakers, who might adopt a population perspective on treatment effect. The probability measures, however, are poorly suited for individual patients who either will or will not experience an event. Furthermore, they only assess the benefits of a treatment within a defined study time frame, which does not apply well to the patients' perspectives, which often comprise both shorter and much longer treatment periods.

To try to overcome these problems Lytsy, Berglund and Sundström proposed an additional way of presenting results from RCTs, namely the 'delay of events' due to treatment (166). The postponement of events has been shown to be an understandable measure for laypersons, possibly related to their motivation to take medication (167).

The main objective of Paper IV was to investigate the beliefs of doctors who commonly prescribe statin treatment. The doctors' willingness to initiate treatment and their anticipation of treatment effect was based on two hypothetical patient cases. Both patient cases were clearly eligible for treatment, and 89.9% and 93.0% of responded that they would prescribe a statin in each case respectively. As impressive as these figures might seem they also reveal that 7.0–10.1% of doctors do not seem to adhere to current treatment guidelines.

One of the main findings in Paper IV was that doctors have an inadequately high or low appraisal of the number of patients likely to benefit from statin treatment over a five-year treatment period. Only about one-third of the respondents had an ARR assessment within an interval supported by evidence-based data. One might argue that having an accurate understanding of the ARR is not necessary for doctors as long as they adhere to the current treatment guidelines. However, if doctors have a misunderstanding they will be unable to provide the correct information to their patients, which consequently makes it difficult for patients to make informed decisions. In addition, there are firm recommendations that clinical research should be used and integrated into clinical practice and, therefore, there is a need to understand it (168, 169).

Most doctors believed that statin treatment would prolong the life of patients such as those in the hypothetical patient cases. There was a considerable range of answers, however, which indicates some uncertainty in this matter. There are no known clinical studies that have followed statin-

treated patients long enough to investigate the treatment's effect on life length. There are, however, several studies that have used existing data from clinical studies to extrapolate the effects on patients' life time perspectives (170-173). Such extrapolations are crude and based on several simplified assumptions, but according to the results reported from them doctors seem to overestimate the effect of statins in terms of gain in life expectancy. The anticipation of statins' effect on life expectancy might be of importance in the clinical situation, when patients are to be informed about the purpose and anticipated effect of statin treatment. Furthermore, the doctors' anticipation of statins' effect on life length was found to be a significant predictor of their willingness to initiate treatment.

Methodological considerations

The studies in this thesis are all cross-sectional studies. This design has several advantages, including being easy to perform at a reasonable cost. The design is also appropriate for comparative analyses. However, it has some limitations, including the difficulty providing evidence that detected associations involve causality. The response rates were in a range that is common in cross-sectional questionnaire studies.

The data were collected by using questionnaires in which the respondents were asked about potentially sensitive issues in their private life. As always with self-reported data there is a risk of report and recall bias, i.e. that the answers given by the respondents do not correspond to the actual situation. This limitation is of extra significance for the assessment of health behaviours. If the respondents have tended to give more socially desirable responses, this would have made it more difficult to detect subgroup differences in many analyses.

The sample of patients taking statins was recruited while patients visited a pharmacy to collect their statin prescriptions. This is a selection procedure based on a behaviour that is an act of primary adherence. For this reason the study population could be assumed be more adherent than the general population of patients who have received a statin prescription by their doctors. However, the group of statin users derived in the population sample were similar in regards to sex, age and medical condition as well as their distribution of the outcome questions. Future research might consider the possibility of investigating views and expectations about statin treatment using a different sampling procedure.

One limitation was that the performed studies did not accurately estimate patient adherence. In 2009, yet another study, initiated by the results in this thesis, was performed in Uppsala county that investigated statin users' beliefs about medication (161). A total of 412 patients responded to a questionnaire about their health situation and beliefs. This questionnaire involved the specific beliefs about health questionnaire as well Morisky's scale of adherence (174), a four-item scale that has previously been used in statin patients (175). According to this study, there were significant associations between adherence and high beliefs in medication.

We acknowledge the possibility of residual confounding effects in patients using statins. This implicates the possibility that patients taking statins and adhering to favourable lifestyle behaviours might avoid premature deaths and might be overrepresented in the sample of patients using statins.

Several of the outcome questions aimed to assess the respondent's beliefs and attitudes. These questions have not previously been used. The outcome questions were, however, phrased as easily as possible without any intentions to frame the answers. The distribution of answers was found to be robust in different populations, and there were high correlations among the different ways of assessing the views about treatment necessity, harmlessness and benefits. To further understand how statin users view their health, risk factors and the expected utility of statin treatment a qualitative approach might provide value. Such a project was started in 2009 with the objective of interviewing 20 patients who had recently started statin treatment after a newly developed myocardial infarction.

Several of the outcome questions regarded uncertainty, and patients and doctors were both asked to assess the benefit of the treatment in probabilistic terms. It is well known that both groups have a statistical illiteracy, i.e. a difficulty or inability to understand numbers (135). This, of course, limits their ability to make rational estimates about the group effect of treatment. However, even an irrational estimate is of interest because it represents the respondent's belief. In addition, we asked respondents about the ARR expressed as the anticipated number of patients that within the study period of five years would avoid a major coronary event. What is asked for then is a natural number, which has been shown to be easier to understand than probability estimates such as a percentage figures (176, 177). Nevertheless, we recognise that when you ask people to express uncertainty in terms of a figure, it will be affected by how the question is phrased.

In Paper IV, the respondents were asked to base their treatment decisions and assessment on two hypothetical patient cases. These cases were carefully chosen to be clinically relevant and correspond to a significant level of aggregated risk, making them eligible for treatment. Yet, they were briefly described, and in a true clinical situation doctors would generally pursue more information through additional investigations. Moreover, the studies used for comparative purposes were meta-analyses, which comprise many studies, some of less relevance in comparison to the patient cases. Thus, such comparisons can seem crude.

In paper IV, the doctors were asked to assess the ARR/1000 and their answers were then categorised as being low, intermediate or high according

to that demonstrated in clinical trials. We chose cut-offs to create groups clearly lower and higher than the interval that corresponds to evidence-based data. Other cut-offs could have been chosen, as well as other comparative approaches.

Main conclusions

The main conclusions from the studies in this dissertation are:

1. People using statins are more concerned about cardiovascular risk factors than people not using statins.
2. Patients using statins have better eating habits in terms of trying to avoid fatty foods and eat more fibre compared with people not using statins.
3. People with poorer exercise and eating habits have a tendency to rate these behaviours as less important for the development of CVD compared with people with better exercise and eating habits. This is true for both statin and non-statin users.
4. People using statins, in general, greatly overestimate the number of patients believed to avoid or delay a myocardial infarction because of treatment with statins for a period of five years.
5. Patients' risk status, including having a history of ischemic CHD, does not seem to be associated with their expectations about treatment benefits.
6. Patients satisfied with their doctor’s explanation of the purpose of the treatment have a greater belief in treatment benefits as well as have a greater belief that statin treatment is necessary and harmless.
7. Patients with an internal perceived health control have a greater belief in treatment benefits and the necessity of treatment.
8. The views about the benefits, harmlessness and necessity of statin treatment are closely related to each other, suggesting that patients use a heuristics approach when assessing their medication.
9. Prescribing doctors have a suboptimal understanding of the proportion of patients that could be expected to benefit in terms of avoiding or delaying a myocardial infarction following statin treatment during a five-year period of treatment.

10. Among prescribing doctors there is a variety of views about statins' ability to prolong life in treated patients. Many doctors believe that statins have a substantial effect on life length both in the primary and secondary setting.
11. Prescribing doctors' views about statins' effect on life length seems to be an important predictor of their willingness to prescribe statins.

Clinical practice implications

The results in this thesis show that patients and doctors have very different perspectives when appraising the preventive treatment of statins. Patients generally recognise that statins have an effect but have difficulty understanding the *size* of that effect. When asked to assess the magnitude of the general effect as an absolute benefit, patients largely overestimate it. This highlights a clinical predicament – patients might expect too much from their medication. However, a correction of patient understanding might weaken their beliefs about the treatment necessity, thereby undermining their adherence to treatment. There is no easy solution to this dilemma, but doctors should be aware that patients might have misapprehensions about what to expect from statin treatment. Nevertheless, patients must be given information adequate for making informed decisions.

The results also show that the rational perspective that physicians use to estimate a patient's overall risk is not associated with how patients anticipate the effect of their treatment. Rather patients seem to appraise statins heuristically, i.e. by intuitive perception. This should be considered in the clinical situation. Patients' beliefs about statin treatment is associated with their satisfaction of the explanation provided by their physician. This highlights the importance of a good patient–physician relationship and a patient-centred care, and suggests that clinicians are important when patients develop their beliefs in treatment and warranted lifestyle interventions.

Furthermore, patients with low social support and patients perceiving their health not to be under their own influence demonstrate a lower belief in the effect and necessity of statins. Consequently, this group might be at higher risk of primary and secondary non-adherence, and could benefit from extra monitoring and support to enhance their belief in the importance of adherence and other warranted lifestyle changes. Generally, doctors should strive to support patient beliefs in specific behaviours because this is believed to increase their likelihood of performing the behaviour.

The results in this thesis also support the idea of the 'generally adherent patient', meaning that adhering to suggested medical treatments is associated with other favourable health behaviours. Adhering to medication and performing favourable lifestyle changes might be other behaviours that

encourage each other, supporting the idea of targeting multiple health behaviours in preventive medicine.

The results of this thesis also provide evidence that prescribing doctors have a suboptimal understanding of statins' effects. Thus, it is important to ensure that evidence-based clinical guidelines are implemented and that doctors are continuously educated.

Summary in Swedish

Bakgrund

Statinbehandling är en mycket vanlig förebyggande läkemedelsbehandling som förskrivs till patienter med förhöjd risk att utveckla symtomgivande hjärt- och kärlsjukdom. Nyttan med denna typ av behandling är väldokumenterad i kliniska studier. Följsamheten till statinbehandling är emellertid låg, vilket utgör ett stort kliniskt problem. Den låga följsamheten väcker frågor kring hur patienter ser på behandlingen med avseende på nödvändighet, risker och förväntad nytta. Vid ställningstagande till behandling med statiner skall patienters totala risk värderas. Det är visat att ju högre risk en patientgrupp har, desto fler individer kan förväntas dra nytta av behandlingen. Det är emellertid oklart om detta medicinska samband mellan risknivå och förväntad nytta återspeglas i patienters syn och förväntningar på behandlingsnytta.

Det saknas kunskap om hur statinanvändare respektive personer som inte använder statiner värderar betydelsen av olika riskfaktorer samt om dessa grupper skiljer sig åt med avseende på hälsobeteenden som kan skydda mot uppkomsten av hjärt- och kärlsjukdom.

Läkare bör ha kunskap om vilken effekt statinbehandling kan förväntas ha hos de patienter de behandlar, vilket bygger på förståelse av de effektresultat som rapporteras från kliniska studier. Det är inte tidigare undersökt vilken effekt som läkare förväntar sig av statinbehandling.

Frågeställningar och metod

Syftet med avhandlingen är att fördjupa förståelsen kring hur patienter och läkare ser på statinbehandling och hur dessa grupper uppskattar nyttan med behandling. Ytterligare syften är att undersöka om patienter med högre respektive lägre risk för hjärt- och kärlsjukdom har olika syn på olika behandlingsaspekter.

De ingående arbetena i avhandlingen bygger på enkätdata insamlat från 829 statinpatienter, 330 läkare och 720 personer 40-80 år från ett befolkningsunderlag. Samtliga undersökningsgrupper kommer från Uppsala

och Gävleborgs län. Statinpatienterna ombads att utifrån sitt egen situation besvara olika frågor kring hur de ser på nödvändighet, risker och nytta med sin statinbehandling. Statinpatienterna respektive befolkningsgruppen svarade på frågor om sina mat-, motions- och rökvanor samt skattade betydelsen av kända riskfaktorer. Dessa faktorer jämfördes mellan grupperna.

Läkare besvarade utifrån två hypotetiska patientfall frågor om de i en jämförlig klinisk situation skulle förskriva en statin till motsvarande patienter. Läkarna uppgav även vilken effekt de generellt förväntar sig hos behandlade patienter, samt vilken effekt de uppskattar att statinbehandling i genomsnitt har på patienters livslängd.

Resultaten från patienters och läkares skattningar av effekten av statiner jämfördes med resultat från kliniska studier. Vidare undersöktes om särskilda faktorer hos patienter respektive läkare var förenade med hög respektive låg tilltro till behandlings effekt.

Resultat och betydelse

Resultaten visar att personer som använder statiner tenderar att värdera kardiovaskulära riskfaktorer som mer betydelsefulla än vad obehandlade personer gör. Patienter som använder statiner är mer måna om att välja mat med lågt fettinnehåll och högt fiberinnehåll jämfört med obehandlade personer.

Patienter som behandlas med statiner har ofta en kraftig övertro på behandlingens sjukdomsförebyggande effekt jämfört med de effektresultat som rapporterats från kliniska studier. Patienters risknivå respektive tidigare kranskärlssjukdom uppvisade inget samband med patientgruppens förväntningar på behandlingsnytta, trots att det enligt kliniska studier finns ett klart samband mellan absolut nytta till följd av behandling och risknivå/tidigare symtomgivande kranskärlssjukdom. Däremot framkom att patienter som är nöjda med förklaringen av sin behandling eller har internt kontrollokus (upplever att hälsan till största del beror på saker som går att påverka) har en högre tilltro till behandlingseffekt. De olika perspektiven på behandling, skattat som syn på behandlingens nödvändighet, harmlöshet och nytta, visade sig vara nära korrelerade till varandra.

Resultaten från läkarundersökningen visar att många läkare har en oklar syn på vilken effekt de kan vänta sig av statinbehandling på gruppnivå. Bara omkring en tredjedel av läkarna uppgav en förväntad behandlingseffekt, till följd av fem års behandling, inom det intervall som stöds av evidensbaserad kunskap. Det fanns en stor variation i läkares uppfattning vilken effekt statinbehandling har på patienters livslängd. Baserat på de hypotetiska

patientfallen svarade läkargruppen att patienter som får primärpreventiv behandling kan väntas förlänga sitt liv med i median två år, och patienter som får sekundärpreventiv behandling kan väntas förlänga sitt liv med i median tre år. Dessa förväntningar förefaller vara höga jämfört med studier som utifrån kliniska effektresultat gjort beräkningar av statiner effekt på behandlade patienters livslängd.

Sammantaget visar resultaten att patienter och läkare har olika syn på flera aspekter av statinbehandling. Statinanvändarna hade ofta en övertro på behandlingseffekt, vilket kan innebära en utmaning beträffande hur detta faktum skall hanteras i den kliniska situationen. Patienter har svårt att förstå resultat från kliniska studier, men har ändå rätt till adekvat information. Till skillnad från hur läkare bör resonera tycks patienters förväntningar på behandlingsnytta inte påverkas av deras egen risknivå. Resultaten visar att patienter som är nöjda med den information de fått från sin läkare har en högre tilltro till sin behandling, vilket tydliggör betydelsen av en god patient-läkarkontakt. Resultaten visar även att personer som tar statiner har flera andra beteenden som är gynnsamma för att förebygga risken för hjärt- och kärlsjukdom. Detta stärker uppfattningen att det är en god strategi att försöka påverka flera hälsobeteenden samtidigt i förebyggande syfte.

Acknowledgements

No man is an island, entire of itself
every man is a piece of the continent, a part of the main.
John Donne (1624)

Many people have in different ways contributed to make this thesis possible, and I would like to express my gratitude to everyone involved.

I would especially like to thank all the informants in Papers I–IV for taking the time and sharing their thoughts about health and statin use. Without you there would be no thesis.

I am also in gratitude to the associations and organisations that believed in the project and granted me financial support. They include The Royal Academy of Arts and Sciences of Uppsala, Uppsala County Association Against Heart and Lung Diseases, Stiftelsen Olle Engkvist Byggmästare, GlaxoSmithKline (Stipendium för Concordance och Följsamhet), Swedish Council for Working Life and Social Sciences (part of project grant) and the Academic Hospital of Uppsala for providing research time (ALF) available within employment.

Ragnar Westerling, my principal supervisor. Thank you for believing in me when I first came and told you about my rudimental research idea. You let me perform the project I always dreamed about. Thank you for also allowing lots of individual freedom combined with constructive criticism and a warm consideration about my personal well being.

My co-supervisor, Gunilla Burell, you joined in a little later on journey, but brought in new knowledge and insights about health belief and determinants of health behaviour. Thank you sharing this with me and, thus, lifting the research to a higher level.

Thank you Bernt Åslund, at the time region officer at Apoteket AB, and thank you all pharmacists in Uppsala and Gävleborg who at the time very professionally and smoothly helped me with the distribution of questionnaires to the population of statin users.

Thank you also to the medical product committees of Uppsala and Gävleborg, who believed in the project and kindly agreed to put their organisations' names on the questionnaires sent out the physicians. I would especially like to thank Åke Schwan, Kerstin Hulter-Åsberg and Agneta

Eklund on the Uppsala committee and Per-Henrik Back and Stefan Back on the Gävleborg committee for sharing their time and offering valuable reflections about the procedure and many of the questions in the questionnaire, thereby improving its final quality.

I would also like to thank Lars G. Nilsson for valuable reflections about the questions used in the population/patient questionnaire as well as kindly providing me access to your network of expertise.

Thank you Lennart Lundin for assisting in the construction of the patient cases as well as valuable feedback in the development of the questionnaire sent out to the physicians.

Thank you Steve Scott Robson for gently, yet firmly, correcting my English through proofreading many of my manuscripts.

At the department there are many people to thank.

Inger Holmström, thank you for combining the role of examiner with warmth and consideration about my situation. Thank you Mats G. Hansson for taking your role as director of doctoral studies seriously and enthusiastically sharing your expertise in ethics. Thank you Marianne Carlsson for firm and understanding leadership. Thank you Johan Hallqvist and Kurt Svärdsudd for always being willing to listen and explain ad hoc queries about epidemiology and methodology.

Thank you all in my research group, in particular Annika Åhs, who introduced me to everyday doctoral student work and over the years has become a good friend. Thank you Marcus Westin, who I have actually shared no less than four workplaces with in the past 12 years. Over the years you have given me good laughs and numerous interesting talks about research as well as just about everything else. You're a true friend. Thank you everyone else in the research team: Ulrica Paulsson, Lars Age Johansson, Stefan Kunkel, Peter Berg and Marianne Hanning for fun and constructive meetings over the years.

Thank you also everyone in my neighbouring research teams including Ulrika Winblad Spångberg, Ellinor Kaminsky, Annika Ernesäter, Mio Fredriksson, David Isaksson, Christina Halford, Clairy Wiholm and Ingrid Demmelmeier for being good colleagues and for contributing to a good research climate.

Thank you Ann-Sophie Hansson and Irene Ekmark for your cooperation in the rehabilitation projects, and Ingrid Anderzén for being a good researcher, a creative force and a good friend.

Thank you to all the administrative staff: Rose-Marie Marcusson, Majbritt Sundelin, Anita Andersson, Charlotte Traneus, Catarina Olsson, Gun-Britt Granberg, Håkan Jansson and Sören Jonasson. You are the backbone of the department.

Thank you Birgitta Lanner and all colleagues at CEOS/socialmedicin at the Akademiska sjukhuset for being good friends contributing with good work environment and stimulating projects.

Thank you Johan Sundström and Lars Berglund for exciting new research cooperation. Thank you Erik Berglund and Ebba Hallberg for being interested in the research area and for offering new knowledge from your master's projects. Thank you Karin Kjellgren and Karin Björkegren for valuable criticism and reflections on my half-time report.

Thank you everyone in my personal network of friends and family, including Robert Bodén and Maria Lundgren and Thomas and Eva Ekelund, and their numerous children. Thank you for fun projects and plenty of memorable eating occasions. Thank you, also, to my parents-in-law, Erik Lundgren and Margareta Andrea, for their support and many memorable moments.

Thank you to my mother, Hillevi Lytsy, for constant support and for always being available, including offering amazing flexibility when it came to taking the train to Uppsala when my family needed it. Thank you to my sister, Anna Lytsy, and family, for fun get-togethers, interesting talks and constant support.

My wife Birgitta Lytsy, without you this thesis would not have been possible. Thanks for always being understanding and supportive about whatever I decide to do. Almost. I love you.

And finally my daughters, Lova, Agnes and Ellinor. Thank you for, so far, showing little interest in your father's struggle for scientific achievement and, therefore, constantly reminding me not to forget what life is really all about.

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Editor: The Dean of the Faculty of Medicine

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