Risk, Risk Analysis and Decision-making with Reference to Biostatistics and the Field of Medicine

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Abstract

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Risk, risk analysis and decision-making are essential aspects of health care and medicine, for patients as well as for physicians and for society as a whole, and the concept of risk and risk analysis in decision-making has a long history. The word risk has many different interpretations and has no commonly accepted definition. In this thesis, we shall let risk stand for the combination of random or uncertain events with negative consequences for human health, life and/or welfare and/or the environment together with some measures of the likelihood of such events. We believe this is the dominant concept and understanding of risk, the risk being the likelihood or probability of an event followed by some negative consequences or activities of that event.

In this doctoral thesis, we focus on biostatistics, risks and risk analysis in the field of medicine, a science which has been using methods from the area of risk analysis for a long time. The seven papers (paper I - paper VII) presented in this thesis, together with a general introduction to risk, risk analysis and decision-making, will be used to illustrate and discuss risk analysis as a tool for decision-making in the field of medicine. From my point a view, risk analysis in the field of medicine aims to reduce pain, raise the quality of life, reduce the risk of adverse events, compare cost efficiency between different treatment regimes and prolong a healthy life. Based on results presented in the thesis, we conclude that biostatistics, risks and risk analysis used in the field of medicine are valuable methods for evaluation of hypotheses within the health care area and a good basis for decision-making.

Keywords: risk analysis, risk, consequence, system, biostatistics, decision, decision-making, health care, medicine

Preface

Risk, risk analysis and decision-making with reference to biostatistics and the field of medicine is the main theme of this doctoral thesis. The thesis consists of seven different papers, each of them dealing with different aspects of risk, risk analysis and/or decision-making in the field of medicine. In addition to these papers, a general introduction to risk and risk analysis is given. This is followed by a brief discussion on the concept of "probability" in risk analysis, and on the role of randomized clinical trials in risk analysis.

List of publications

This thesis is based on the following original papers, which will be referred to by their Roman numerals:

I. Näsman P., Örtendahl M. (2007).
    Perceived consequences among pregnant and non-pregnant women of continuing or ceasing to smoke.
    International Journal of Gynecology and Obstetrics, Volume 99, Issue 2, pages 117-121, Nov 2007.

II. Näsman P., Örtendahl M. (2007).
    Values and beliefs about consequences related to smoking among pregnant and non-pregnant women.
    Journal of Obstetrics and Gynaecology, Volume 27, Issue 6, pages 558-563, Aug 2007.

III. Ahmed N., Näsman P., Wahlgren G. (2000).
    Effect of intravenous nimodipine on blood pressure and outcome after acute stroke.
    Stroke, Volume 31, Issue 6, pages 1250-1255, June 2000.

IV. Hedenus M., Birgegård G., Näsman P., Ahlberg L., Karlsson T., Lauri B., Lundin J., Lärfars G., Österborg A. (2007).
    Addition of intravenous iron to epoetin beta increases hemoglobin response and decreases epoetin dose requirement in anemic patients with lymphoproliferative malignancies: a randomized multicenter study.
    Leukemia, Volume 21, Issue 4, pages 627-632, April 2007.

V. Allgulander C., Näsman P. (1991).
    Regular hypnotic drug treatment in a sample of 32,679 Swedes: associations with somatic and mental health, inpatient psychiatric diagnoses and suicide, derived with automated record-linkage.
    Psychosomatic Medicine, Volume 53, Issue 1, pages 101-108, Jan/Feb 1991.

VI. Rehnqvist N., Hjemdahl P., Billing E., Björkander I., Eriksson SV., Forslund L., Held C., Näsman P., Wallen NH. (1996).
    Effects of metoprolol vs. verapamil in patients with stable angina pectoris. The Angina Prognosis Study in Stockholm (APSIS).
    European Heart Journal, Volume 17, Number 1, pages 76-81, Jan 1996.

VII. Nilsson C., Linde A., Montgomery SM., Gustafsson L., Näsman P., Blomberg MT., Lilja G. (2005).
    Does early EBV infection protect against IgE sensitization?
    The Journal of Allergy and Clinical Immunology, Volume 116, Issue 2, pages 438-444, Aug 2005.

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The warm and friendly atmosphere within the Center of Safety Research, no matter what department it belonged/belongs to, has made my work extremely pleasant and I am grateful to everyone I worked with during my time at the Royal Institute of Technology. It has been a very good time for me and I have really enjoyed being a part of the Center of Safety Research.

All the seven papers presented in the doctoral thesis have been published earlier in peer-reviewed international journals and I would like to thank the publishers, the editors of the journals, the anonymous referees, my fellow workers, all my colleagues and co-writers within the different studies and projects that are reported in the papers. It has been a pleasure working together with you all and I hope we can work together in some constellations in the future as well.

Stockholm, June 2010

Per Näsman

Contents

Risk, Risk Analysis and Decision-making with Reference to Biostatistics and the Field of Medicine

Introduction

In our daily life, all of us are surrounded by different kinds of risks and we constantly strive for better methods to find and quantify them, and by extension, manage these risks. Every activity involves risks, of which some we are willing to accept and others we are not. We all like to live a life that is free from risks, but that is impossible.

William D. Rowe states in the introduction to his book An Anatomy of Risk[1]

"The only certainty in life is death; uncertainty lies in when and how death occurs, and whether it is final. Man strives to delay its onset and extend the quality of life in the interim. Threats to these objectives involve risks, some natural, some man-made, some beyond our control and some controllable. As the length and quality of life have increased, and thereby its value, society has become increasingly concerned with avoiding risks, particularly those imposed without offsetting benefits to the risk taker".

Risk, risk analysis and decision-making are essential parts of health care and medicine, for patients as well as for physicians and for society. Gretchen B. Chapman and Frank A. Sonnenberg state in their abstract in Decision-making in Health Care[2]

"The physician has to determine what is wrong with the patient and recommend a treatment, while the patient has to decide whether or not to seek medical care and whether to go along with the treatment recommended by the physician. Health policy makers and health insurers have to decide what to promote, what to discourage, and what to pay for".

Nowadays, the health care system is without any doubt discussed in almost every country and after the turn of the century, concerns about costs, accessibility and quality of health care have substantially risen. Treatment for a broad spectrum of diseases has become much more effective and available, thanks to great advances in sciences such as chemistry and biology, a better understanding and knowledge of the different diseases, great progress in medical technology and pharmaceutical development, and new surgical techniques for preservation and replacement of tissue and organs. However, increasing treatment options continue to result in a growing number of choices and demands from the patients to take advantage of the new health care regimes. This, of course, raises many questions about health and the health care system.

As early as 300 B.C. the Greek anatomist and surgeon Herophilus[3] stated

"To lose one's health renders science zero, art inglorious, strength unavailing, more wealth useless and eloquence powerless".

Risks in the field of medicine have always been a topic of interest for us and I think this is mainly because the ultimate outcome is death. My belief is that many of us in many ways have an unclear and undeveloped conception of death and I think this is well reflected in what the American film producer and actor Woody Allen once said

"I am not afraid of death; I just don't want to be there when it happens".

During the past decade, many studies have been carried out on risk-related topics, and society has showed a significant interest in the field of risk analysis. Risk analysis is the interdisciplinary field of science that combines results and knowledge of probability theory, mathematical statistics, statistics, engineering, medicine, philosophy, psychology, economics and other applied disciplines. Risk analysis is a well established tool with a long history in the areas of technological risks and in the field of medicine.

The concept of risk and risk analysis in decision-making also has a long history and Terje Aven gives an enlightening example in his book Foundations of Risk Analysis[4] where he quotes from Pericles' Funeral Oration in Thucydides' History of the Peloponnesian War (started in 431 B.C.).

"We Athenians in our persons, take our decisions on policy and submit them to proper discussion. The worst thing is to rush into action before consequences have been properly debated. And this is another point where we differ from other people. We are capable at the same time of taking risks and assessing them beforehand. Others are brave out of ignorance; and when they stop to think, they begin to fear. But the man who can mostly be accounted brave is he who best knows the meaning of what is sweet in life, and what is terrible, and he then goes out undeterred to meet what is to come".

The word "risk" derives from the early Italian "risicare" which means "to dare". Risk has many different interpretations and there is no commonly accepted definition. In our context, we shall let risk stand for the combination of random or uncertain events with negative consequences for human health, life and/or welfare and/or the environment together with some measures of the likelihood of such events. I believe this is the dominant concept or understanding of risk, the risk being the likelihood or probability of an event followed by some negative consequences or activities of that event.

In risk analysis, one tries to recognize the nature of various risks and to assess their magnitude. One of the major issues in risk analysis is to define and know what system to consider and in many cases this is not self-evident. The situation is clearly different for planning and/or building a system compared with running the same system in real time. The system that is going to be the

subject of the risk analysis must be clearly defined and the limitations and the boundaries of the system must be set. It is important to ensure that everyone involved in a risk analysis has a common understanding of the system being considered, including relevant operations. This is especially critical in the field of medicine since the individual patients and the health care system might not have the same goals for the measures and the decisions taken.

There is no universal way to describe the system which is to be studied in a risk analysis. Gustafsson[5] claims that the formal system description must include four parts:

- Description of the system, including the relevant operations and phases

- Statement of the period of time to which the analysis relates

- Statement of the personnel groups, the external environment and the assets to which the risk assessment relates

- Capabilities of the system in relation to its ability to tolerate failure and its vulnerability to accidental effects.

Defining the system will reveal information on what is going to be included in the analysis: components, subsystems, process, time-spans, functions, etc. A complete risk analysis of a system has to include all of its life cycle phases. This will help the decision-makers, giving them the best foundation on which to base their decisions.

For risk analyses in the field of medicine, it is crucial to understand what system to study. Not all patients may be appropriate for inclusion in the risk analysis in question. This is the case in clinical trials. It is central to specify the patient population which is to be studied in the risk analysis in order to define the population thoroughly for the analysis in question. To be able to render the patient population well defined one has to develop and use specific inclusion and exclusion criteria. This is well reflected in the seven papers (paper I - paper VII) presented in this thesis. In all of the papers, different inclusion and exclusion criteria are used to specify the patient population to be studied and this allows us to improve the power of the statistical inference from the population studied to the total patient population fulfilling the same criteria. As can be seen in the presented papers, the specific inclusion and exclusion criteria vary between the different risk analyses and this, of course, affects the inference. For example, the patient population studied in paper IV is more specified and specific than that in papers I and II. The patient population studied in paper IV is also more specified and specific than those in papers III, V, VI and VII.

Furthermore, it is important to understand that the medical and statistical inference drawn from a risk analysis in the field of medicine is heavily dependent on the definition of the patient population used in the risk analysis. This is reflected, for example, in the discussion in papers I and II, in which a patient population from Bulgaria was examined. The fact that the patients came from Bulgaria may or may not affect the quality of the inference from the risk analysis.

When the phase of defining the system is completed, there are five major steps in a general risk analysis:

1. Risk identification

2. Risk estimation

3. Risk perception

4. Risk valuation

5. Decision

The first step, risk identification, is to pose questions like "what can happen" and/or "what can go wrong that could lead to the occurrence of a hazard exposure". Since risk identification is non-numerical by nature, methods like a think-tank are recommended and widely used. A problem with risk identification is that risk sources may be overlooked for the simple reason that they have not resulted in any accident so far. Failure to identify important sources of risk will lead to an underestimation of the total risk and may be the explanation for some accidents, accidents that might be fatal. One also has to try to describe the possible connection between causes and consequences. In real life, it is quite impossible to describe a system so well that it will cover every possible situation. Simplifications will have to be made.

The second step, risk estimation, is to estimate the risks and the likelihood of the different events and/or outcomes. This can be done with statistical methods and/or risk analysis methods. Risk estimation is referred to by many researchers as Probability Safety Assessment (PSA). Kopustinskas[6] states "it should be understood that any risk estimation contains limitations and a certain degree of subjectivity". Different ways of risk estimation based on models, probabilities and/or risk measurements will be discussed further in the chapter "Some basic concepts of models and probability in risk analysis" in this thesis.

Most human activities and many natural phenomena are possible sources of risk and Kopustinskas[6] groups the types of risks into three groups:

<u>Natural hazards.</u> This type of risk includes all naturally occurring phenomena (e.g. earthquakes, storms, floods, volcanic eruptions, drought, lightning etc.) that can have a direct impact on humans and may also increase the likelihood of accidental hazards from fixed installations or network systems.

<u>Accidental hazards.</u> This type of risk is mainly caused by accidents in various human activities, including industry, transportation, waste disposal facilities and others. Severe accidents may have serious consequences for the public and the environment.

<u>Continuous hazards.</u> Continuous emission to air, water and land from industrial, commercial or residential activities is the last type of hazards. A transportation network, including vehicle emissions, is one example of continuous hazards.

The third step in the risk analysis, risk perception, is the way we perceive the risks. Risk perception is associated with the psychological aspect of risk and this is essential to understand when we interpret and try to understand the risks. Risk perception is also important in public risk communication. The psychology of risk is closely related to the question of what is an acceptable risk. The term acceptable risk is a complex issue, which involves not only technical assessments but also the values of societal beliefs and societal risk acceptance. Risk only makes sense if it is perceived by someone.

The fourth step, risk valuation, is to value the risks and to find possible ways of controlling and reducing them. The valuation of the risks is always tied to risk perception. Mankind often appears to be reluctant to accept new technology. This resistance is often based on the fear that use of the new technology implies potential losses, which can be monetary losses, human life losses and/or environmental losses. This fear is related to the lack of experience of the technology and the fear tends to decrease as experience in the use of the technology in question increases. Fear in this context refers to the risks we believe are involved with usage of the new technology. However, we are willing to take these risks when we gain benefits and have the freedom to choose, e.g. flying, hill climbing, or smoking. We tend to accept larger risks when it is a free choice rather than imposed from the outside, e.g. hill climbing as opposed to radiation [7].

After going through the first four steps of the risk analysis, different decision alternatives should be compared with respect to the results of the risk analysis together with the benefits and the costs as a basis for the decision.

Examples of two different schemes for risk analysis can be represented by the following two figures, 1 and 2.
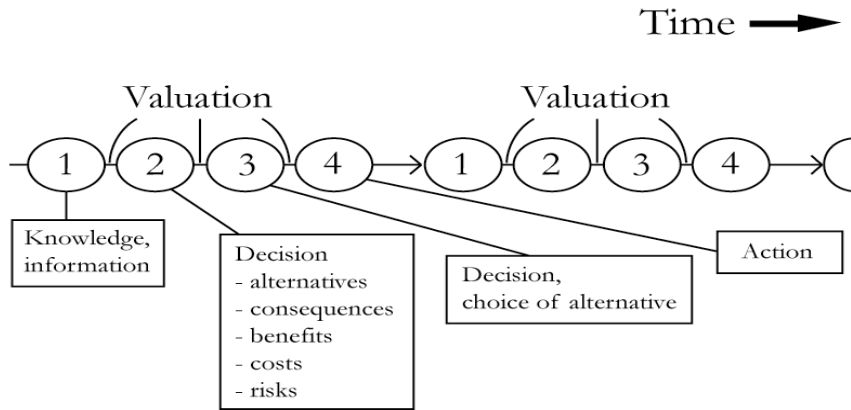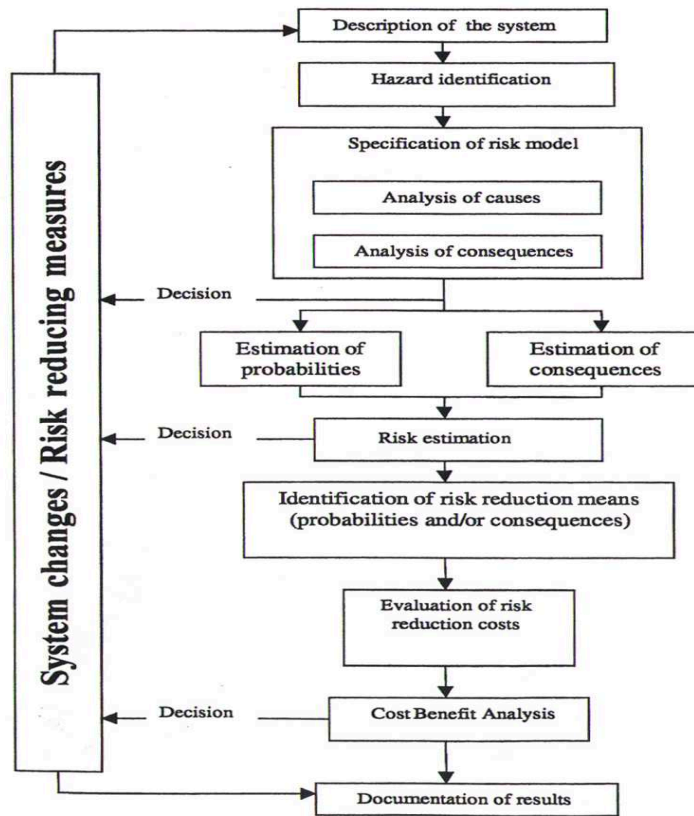
Figure 1. Risk analysis chain, adopted from Näsman[8]

Figure 2. Risk analysis, adopted from Bäckman[9]

One of the key questions in risk assessment is *how safe is safe enough?* This is primarily connected to the concept of risk and it is strongly dependent on the benefits someone receives by taking a certain risk. One of the ways to set up an acceptable risk level is to try to compare different kinds of risk. Many sources provide information on risk from different hazards but, of course, the estimates of risk may differ depending on the initial data and statistics used.

However, if one tries to take into account most of the possible effects of a decision, it might lead very far. For example, when comparing different ways of producing energy, it has been proposed that risks in producing material for the energy plant as well as possible negative effects from waste material in the far future should also be included. Due to the long time span, the long-term consequences are difficult to study in this case. The same could be argued about building constructions, for example, which might have a life length of several hundred years. The question of global warming is another example of the same kind. Again, it is critical to clearly define the system that is going to be the subject of the risk analysis, and the limitations and the boundaries of the system must be carefully set. Although there might be some fundamental factors that all risk analyses have in common, the nature of applications can be entirely different. Compare, for example, the safety of a transportation network and the safety of a nuclear power plant including its nuclear waste.

Risks are always connected with some type of decision; the choice between different alternatives and the last step in the presented risk analysis scheme, the decision, is far from unproblematic. Rowe[1] states

"Decisions in a pluralistic society are made in myriad institutions, public and private. Identifying the decision makers (individuals, groups, institutions) is at least as problematic as determining how a decision is reached".

Decision-making involves three groups, more or less separated: the decision makers, the cost and benefit takers and the risk bearers.

This doctoral thesis focuses on risk analysis in the field of medicine, a science which has been using methods from the area of risk analysis for a long time. One of the basic concepts in the field of medicine is *the randomized clinical trial* (paper I - paper VI) which will be briefly described later in the thesis. We will also later in the thesis describe the meaning and use of probabilities in the risk analysis (papers I, II, and V). But no matter how many clinical trials are performed and no matter how high their quality is, they will never address more than a small fraction of the knowledge needed for clinical practice. Even in areas well covered by clinical trials, the patients or the population may differ from the conditions in the trial such that the correct decision will not be clear (papers I, II, VI, and VII). For these reasons, decision modelling will be increasingly important. Risk analysis and decision-making research focuses on the role of uncertainty in health care. More efficient methods of computing probabilities and increasing computing power will also increase the possibility

of applying these methods to more and more realistic scenarios. The further development of large-scale databases (paper V) will also help risk analysis and decision-making in the field of medicine even though there are some potential problems with this type of database. This includes the art of collecting information and the type of collected information, control of confounding factors and low statistical power for events with low frequency (paper V).

From my point of view, biostatistics and risk analyses in the field of medicine aim to reduce pain, raise the quality of life, reduce the risk of adverse events, compare cost efficiency between different treatment regimes and prolong a healthy life. All this has a prominent role in the seven presented papers.

Objectives

In this thesis we will focus on risk, risk analysis and decision-making with reference to biostatistics and the field of medicine. However, much of what will be said will also be valid for risk analysis in other areas. Each of the presented papers is chosen in order to present different aspects of risk analysis within the area of biostatistics and the field of medicine.

Paper I examines the perception of the risk of smoking-related psychological and social outcomes, and the effect of pregnancy and the intention to stop smoking on the perceived risk. The paper is mainly presented in the thesis in order to discuss in what way the studied patients can be said to reflect the total population of female smokers.

Paper II tests a model based on the product of value and belief, called expected utility (EU), on the addictive behaviour of smoking. This paper is based on the same patients as paper I. The study also includes the use of subjective probabilities.

Paper III attempts to confirm a correlation between nimodipine-induced reduction in blood pressure (BP) and an unfavorable outcome in acute stroke with and without adjustment for prognostic variables and to investigate the outcome in subgroups with increasing levels of BP reduction. The study is a follow up study of a study that was terminated after inclusion of about half the planned number of patients due to indications of neurological worsening of the treated patients.

Paper IV presents a randomized study assessed to find if intravenous iron improves haemoglobin response and permits decreased epoetin dose in anemic, transfusion-independent patients with stainable iron in the bone marrow and lymphoproliferative malignancies not receiving chemotherapy. The main reason for presenting the study in the thesis is to discuss the significance of using a well defined patient group in a risk analysis. The paper also present results for a cost-benefit analysis.

Paper V studied Swedish survey responders who reported regular treatment with hypnotic drugs, to find associations to perceived health problems, inpatient psychiatric diagnoses, and subsequent suicide. Among 32,679 sampled Swedes, 26,952 (83%) participated, 500 of whom (2%) reported regular hypnotic drug treatment. The rate of treatment was higher in women, and increased by age in both sexes. The paper is a well presented study marking the importance of good databases for risk analysis.

Paper VI studies long-term treatment effects of metoprolol or verapamil on combined cardiovascular end points and psychological variables in patients with stable angina pectoris. The implications following when we base risk

analyses on long-term studies is the motive for inclusion of the paper in the thesis.

Paper VII investigates whether there is a relation between the serostatus of 13 different viruses and parentally reported infections and IgE sensitization in 2-year-old children. The motive for including the paper in the thesis is that the study is based on a non-random sample of patients and the study also used self-reporting as a way of collecting data. The effects of this must be discussed in a risk analysis.

Risk analysis methods

There are several different methods within the field of risk analysis. Many of these methods can, furthermore, be used in different ways depending on the purpose of the risk analysis. The first steps in the risk analysis are almost always of a qualitative nature i.e. describing the system, identifying the hazards and specifying the causes, and modelling the risks is certainly of a qualitative nature. But then after the system to be studied is set, there are a variety of ways to go and the risk analysis will, of course, be dependent on the way one chooses to go.

Lindberg, Thedéen and Näsman[10] state at least three different methods of application that can be of interest to choose among and within:

a) Preliminary hazard analysis or detailed hazard analysis. In many cases, a preliminary analysis may be sufficient and it might be enough to work with rough and easy-to-grasp risk, cause and effect categories whereas other problems require a more detailed analysis broken down to the lowest possible level. A detailed analysis of the different components' service life length and fault probabilities might be necessary (papers I and II).

b) Qualitative or quantitative analysis. As mentioned above, the first step in all risk analyses, the task of describing the system, is of a qualitative nature, as is identifying the hazards. If the purpose of the risk analysis is to identify risk sources and the risks within the given system under study, a qualitative analysis could be sufficient. If, on the other hand, the aim is to estimate numerical values of the risks, one has to use quantitative methods. The quantitative methods allow us to estimate probabilities for the events of interest. Examples of this are calculating accident rates and survival probabilities, and with the help of confidence intervals, hypothesis testing, risk and odds ratios, we can compare different groups (papers I - VII).

c) Inductive or deductive analysis. In some cases, the data and the data sources are sufficient in order to be able to use statistical methods and statistical analysis for the estimation within the risk analysis (paper V). In cases where no data are given, one is forced to work deductively, to generate commencement material for the risk analysis. In the majority of cases, the risk analysis comprises inductive as well as deductive parts, so in a practical situation it is necessary to use both ways (papers I, II, III, IV, VI and VII).

The different risk analysis methods can then, according to Lindberg, Thedéen and Näsman be divided into three groups depending on the type of objects they are designed to analyse: technical systems, organizational risks and human reliability[10].

Table 1 shows the breakdown the authors[10] used in their report.

Method	Short description
Technical systems	
Fault tree analysis - FTA	Analysis of the causes of a given incident
Event tree analysis - ETA	Analysis of alternative consequences of a given event
Failure modes and effects analysis - FMEA	Analysis of faults of technical components
Hazard and operability study - HAZOP	Analysis of possible risks/disruptions in processes
Maximum credible accident - MCA	Analysis of worst possible consequences
Organisational risks	
Management oversight and risk tree - MORT	Organisational demands are compared with actual organisation
Administrative safety analysis	Organisational conditions are judged according to form
Human reliability	
Work safety analysis	Working conditions are analysed
Action error analysis - AEA	Analysis of dangerous divergences from pre-specified working procedures
Human reliability analysis - HRA	Analysis of human inclination to act erratically during certain working tasks

Table 1. Some examples of risk analysis methods, adopted from Lindberg, Thedéen and Näsman[10]

The list in table 1 contains examples of the methods used in risk analysis and there are many variants and methods not described here. For a review of more variants and methods, see for example Rausand[11].

In Lindberg, Thedéen and Näsman[10] the authors also give a more comprehensive description of the different methods and, furthermore, the report presents methods to analyse the interaction between man, technology and organisation within the field of risk analysis.

In the field of medicine, the risk analysis is often based on *clinical randomized trials*. In the last five to seven decades, research in the area of medicine has grown immensely, and this growth has seen ever-increasing attention to, and awareness of, the importance of randomized clinical trials. The randomized

clinical trial has evolved into a powerful tool that has provided the evidentiary basis for many of the advances of, and within, modern medicine.

Clinical trials often compare experimental treatments with established treatments and/or a placebo, a medication without the active ingredient of the drug being studied (paper III, paper IV, paper VI).

Randomization is an essential part of the clinical trial design. In order to ensure that the actual trial is as fair as possible and does not include any bias, volunteering patients who meet the established inclusion and exclusion criteria are chosen at random for membership in the experimental group: the participants who receive the new treatment, or the control group, the participants who receive the placebo or standard treatment. Randomization is used in the presented papers I to VI. Papers I, II and V include patients chosen at random at a given time. In papers III, IV and VI, the included patients are randomized to the different treatments in a defined way.

Note that the physician and the researchers administering the study have, in most cases, no knowledge of a patient's group placement during the trial (papers III and VI). But, as mentioned earlier in the thesis, not all patients are right for all types of clinical trials. All clinical studies have to have specific inclusion and exclusion criteria to render the patient population well defined for the clinical trial in question. This is because we wish to maximize the power of the study.

The medical clinical trial then slavishly follows a fixed protocol which is the study plan on which the clinical trial is based (papers I, II, III, IV, VI, and VII). The protocol is established with extreme care and designed to protect the life and health of the participating, volunteering, patients as well as answer the specific research questions within the study. The protocol contains, for example, a description of the types of people that may participate in the trial, the schedule for measurements and tests, test procedures to be used, medications, concomitant medications and dosages. The protocol should also state the length of the study, and under what conditions and circumstances the study may be interrupted. Patients participating in clinical trials are seen regularly to monitor their health and to determine the safety and effectiveness of their treatment.

As can be seen, the randomized clinical trial follows a well-established system. The system is designed to ensure both the well-being of the patients and the scientific validity of the study. The randomized clinical trial has indeed lifted medical research from an anecdotal approach that was in general use before the mid-twentieth century to a new and improved level. Nowadays, the clinical randomized trial design is a standardized design and the result from a clinical randomized trial will achieve good reliability and efficiency. For the future, one of the most important tasks is the ongoing work with good clinical practice

(GPC) and improvements in the protocol management. Working on improving diagnostic and therapeutic quality is critical, and standardized guidelines and standardized protocol will certainly assure further success in the area of interest.

Data and data sources for risk analysis

Data of good quality and the accessibility of data are crucial for a risk analysis. This is stressed upon in the majority of the papers presented in this thesis and is especially the case in paper V where we utilize existing registers and databases for the risk analysis.

In earlier times, when new medical regimes and/or technical innovations were gradually introduced, one could gain empirical experience and acquire data about how often different events occurred, for example the number of different kinds of accident or the number of infected and/or dead individuals from a specific illness. This data could then be used in the risk estimation. Nowadays, many systems are built in large and often unique units. In cases like this, it is no longer possible to rely on professional experience. We have to use the structural mechanics and other logical models in the system and computer programs to do the risk calculations. This is particularly the case in the planning and construction phase of the life cycle. The physical system corresponds to a logical system, consisting of a number of components, and the functioning of the components will determine whether the system collapses or not. The new area in medicine dealing with genetics, and its influence on illness and disease is an example of a system of this kind. Due to the type of system studied, we need different kinds of information to be able to estimate the probabilities or likelihood of events happening in the system. There are three steps on the information staircase presented by Grimvall et al.[12] (figure 3).
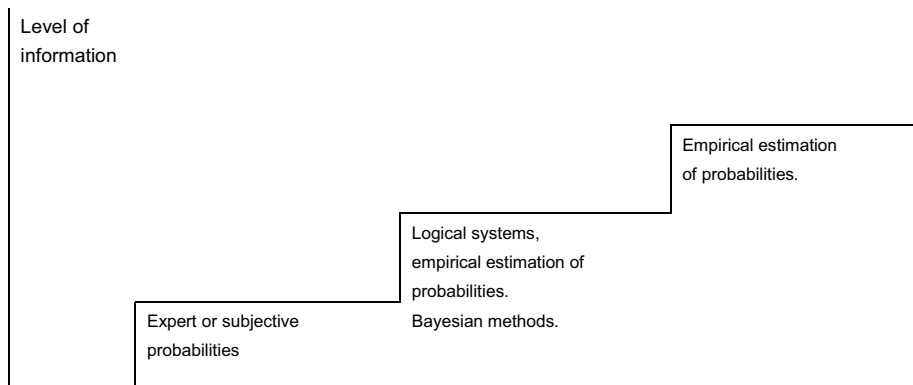

Figure 3. The information staircase, adopted from Grimvall et al[12].

- In areas where there are many data available, one can use ordinary statistical methods to estimate the probability or likelihood of the different events. The ideal situation is one in which a stable time series gives the number of occurred events.

- The middle step, the second one, has few data but the estimation can be based on a logical system. Knowledge of the components in the logical system can be combined with empirical estimators of the probability or likelihood. Bayesian methods can be used to calculate the probabilities, based on experts and the events that occur.

- On the first step, there are no data at all. In this case, experts can be used to help estimate the risks and their subjective probabilities of the events occurring can be used in the risk analysis.

Lack of data within a risk analysis causes problems. There is, for example, a problem trying to analyse railway safety with statistical methods. Few accidents occur and it is difficult to obtain reliable estimates of the expected number of fatalities per year. One possible way of solving the problem with lack of data would be to report incidents in detail and to use this incident data for statistical analysis. It would be profitable for the area of risk analysis if both accident data and incident data together with adequate appurtenant information were collected in a formal way and stored in a database easily accessible to the researchers.

However, in the field of medicine in Sweden, one has come quite a long way in building different kinds of registers and databases (paper V). Statistics of diseases and surgical treatments of patients have a long history in Sweden: data of this kind have been published for more than 100 years and have been available for the whole of the twentieth century. Registers and databases of this kind are well suited for use in risk analysis. The National Board of Health and Welfare (Socialstyrelsen) administers many of the registers in the medical area, among them, the National Patient Register. From 1987, the National Patient Register covers all public, inpatient care in Sweden. The Centre of Epidemiology also has data from earlier years and today the register includes 50 million discharges for the period 1964-2006. This register was used in paper V, together with the Causes of Death Register and the survey "Living conditions" made by Statistics Sweden. The Causes of Death Register was also user in paper VI.

Due to the existence of all these registers and the good data quality within them, a great deal of research can be based on them and medical science has certainly gained from this. For example, research within the area of cancer has been able to utilize the Swedish Cancer Registry; the register allows cancer research to flourish and it forms the basis of many relevant hypotheses to test in

the risk analysis. The existence of good registers and databases also makes it possible to apply more powerful statistical methods in the risk analysis. Examples of such methods are different kinds of regression analysis and multivariate methods (papers II, III, IV, VI and VII). Experimental design and analysis of variance will help to understand the model behind the risk analysis at hand. If we have a good knowledge of the registers, the databases and the measurements taken will give us better tools to estimate the influence of different variables in the risk analytic models and also give a better understanding of the mechanism of the model and knowledge of the interactions and correlations between the measured variables.

Some basic concepts of models and probability in risk analysis

In risk analysis, it is essential to know the probability of one or more events. The following gives an introduction to some aspects of models and probability and explains some important concepts of probability theory. Instead of presenting strict mathematical expressions, the concepts will be illustrated with calculations for a number of specific cases.

Models

The concept of a model is of pivotal importance to risk analysis. A model is an idealised description of a certain occurrence, representing its essential properties without including all the details. A distinction is made between analogue models (e.g. maps, construction drawings or ball-and-stick models of matter where the balls represent atoms), physical models (e.g. a 1:75 scale cardboard model of a house, or the use of crash test dummies instead of real drivers in a car crash test) and abstract models. Abstract models are often used within technology and natural science. They can be deterministic or stochastic. Another name for a stochastic model is a random model.

In a deterministic model, occurrences are approximated with mathematical functions. One example of a deterministic model is Ohm's law, $U = I \cdot R$. Another example is if we want to determine the area of a circular ice rink. We picture the ice rink as a circle with the area πr^2, where r is the radius of the circle. This is obviously a model, as there are no ice rinks with the shape of an exact circle in reality; they only exist in an abstract world. Yet another example of a deterministic model is the use of classical mechanics to describe how an object falls down due to gravity is. A common property of all deterministic models is that occurrences are approximated and expressed with mathematical functions.

In probability theory, random models (stochastic models) are used when describing random experiments. By random experiment, we mean experiments that are repeatable under similar conditions and for which the results are not predictable, even when these experiments have been conducted many times before.

A typical example of a random experiment is rolling a dice. Beforehand, we do not know what value we will get. Another example is a lottery. We do not know in advance if the lottery ticket will win a prize. Yet another example is radioactive decay. The exact number of particles that will decay during a certain period of time cannot be predicted. Before probability theory can be applied to these cases, a random model describing the unpredictable variation must be formulated.

Probability

One definition of the concept of probability can be based on an essential property of random trials. For example, suppose we roll a fair die a large number of times. After every throw we calculate the relative frequency of sixes, i.e. the ratio of the number of rolled sixes and the total number of throws. This relative frequency will be more and more stable and approach $1/6 = 0.166666\ldots$ as the number of throws increases. If the die is not fair, but is crooked, showing some kind of distortion, the frequency will approach another value, which is impossible to guess beforehand.

We can now define the probability of a rolled six as the obtained relative frequency when the number of throws approaches infinity. This definition has the advantage of being in accordance with what most people mean by probability, but it will lead to problems in cases where it is not possible to make repeated independent trials. If, for example, we want to determine the probability that a newborn baby girl will live for at least 90 years, we can collect empirical material. The relative frequency in the collected material of women being older than 90 years can be used as an estimation of the probability. With this kind of estimation of probability, the accuracy of the model will be highly dependent on the size of the collected material. In this thesis, many of the calculated probabilities are of this kind (papers I --VII).

Another similar definition of something that is usually called probability, but should be called risk measurement, is used, for instance, in some parts of the transport sector. The risk measurement is calculated by relating a number of occurred events to some sort of traffic workload. In railway traffic, the number of killed and injured passengers per billion passenger- kilometre is used as a risk measurement. For motor traffic, one measurement of the risk of being killed as a car passenger is calculated by relating the number of dead passengers to the number of passenger kilometres. One must carefully consider what to use as a denominator and numerator when calculating these types of risk measures. It is not obvious what should be the denominator when calculating, for instance, a risk measurement for flight safety. Should it be the number of flights or the number of flying hours? The choice of denominator and numerator will, of course, determine the size of the risk measurement.

The concept of probability can also be given a subjective content (papers I, II and VI). The word is used in everyday language about events that are not possible to characterize as random trials. It is not possible to claim that a Swedish curling team will have a probability of 90 % of winning the gold medal in a future Olympic game. Yet another example of subjective probability is this kind of statement: "The risk that a certain share will fall during next week is at most 10 percent". Of course, neither of these individual cases allows any interpretation in terms of frequency, as they are based on unique situations and conditions that are not repeatable.

At present, there is considerable interest in subjective probabilities and much has been written on this topic in the scientific literature. The subjective probabilities can play a significant role in risk analysis, as input values in larger complex models. Bayesian methodology can be used to continuously revise the probabilities used as input values in the model, as more data is obtained. In Bayesian methodology, the basis is a probability distribution estimated beforehand, the *a priori* distribution. This distribution is then recalculated, using obtained data, to an *a posteriori* distribution.

The advantage of Bayesian methodology is that it is applicable within areas with small numbers of occurred events, i.e. where little data is available. The *a priori* distribution in these cases can be obtained by expert judgement. The few data on events or incidents that may be available can later be utilized to determine the *a posteriori* distribution. Bayes' theorem gives us a way to apply quantitative reasoning. When several alternative hypotheses are competing for belief, we can test them by deducing consequences of each one and then conduct experimental tests to observe whether or not those consequences actually occur. If a hypothesis predicts that something should occur, and that actually happens, it strengthens our belief in the truthfulness of the hypothesis. Conversely, an observation that contradicts the prediction would weaken our confidence in the hypothesis. In Bayes' theorem terminology, we first construct a set of mutually exclusive and all-inclusive hypotheses and spread our degree of belief among them by assigning a prior probability to each hypothesis. If we have no prior basis for assigning probabilities, we could just spread our belief probability evenly among the hypotheses. Then we construct a list of possible observable outcomes. This list should also be mutually exclusive and all-inclusive. For each hypothesis, we calculate the conditional probability of each possible outcome. This will be the probability of observing each outcome, if that particular hypothesis is true. For each hypothesis, the sum of the conditional probabilities for all the outcomes must add up to one. We then note which outcome actually occurred. Using Bayes' theorem, we can then compute revised *post priori* probabilities for the hypotheses.

Statistical inference

In a statistical analysis, a population is studied in some respect. The concept of population denotes a set of elements having one or more properties in common.

A population is a set of data, or in other words, a set of observations. In a census, the whole population is studied. Censuses are of great significance in the production of official statistics, where information regarding, for instance, the number of births, and the number of deaths are collected (papers V and VI). Censuses are used by industry as well, for instance in the inspection of valuable or potentially dangerous products.

However, a census is often too costly and time consuming. It can even be unrealistic to carry out. This applies to destructive testing. If a census of crash tests of cars were required, all cars would be destroyed during the tests.

Instead of a census, a sample survey is often conducted, where only a part of the population is studied. The result from the sample is used to draw an inference about the population (papers I, II, III, IV, VI and VII).

The certainty of the inference depends on, among other things, the sampling method and on the size of the sample (papers I, II, III, IV, VI and VII). One example is the pre-election polls continuously being conducted with the aim of estimating the proportion of people voting for different political parties in order to predict the final outcome in the next general election. This type of survey is conducted in connection with elections all around the world.

Questions concerning relationships among variables are also well suited to study with the use of sampling methods (papers I, II, III, IV, VI and VII). Do men have a more positive attitude than women to nuclear power? Is there a tendency for people with higher incomes to prefer a certain political party? Does the age of an individual influence his or her attitude to refugees? If there is a relationship among variables, this is called a correlation. However, one has to be cautious about relationships. It is not certain that it is causal; it could be a spurious relationship.

When drawing inferences about the whole population from the result in the sample, there is a risk of making systematic errors as well as random errors. The systematic error (bias) is constant and may be due to the use of a faulty measuring instrument, for instance, a scale that has been wrongly calibrated, thus constantly showing 1kg too much. Misleading and vague questions in a questionnaire can also result in systematic errors.

The random error is a random variable with the expected value zero. Therefore, we can estimate the size of the random error by statistical methods. This is done and is presented in uncertainty intervals (confidence intervals) for the quantity in question (papers I - VII). It is also popularly called the margin of error. One important and interesting observation is that the more times a trial is repeated, the narrower is the confidence interval for an estimation of a property. This is due to the law of large numbers, which states that the average of several independent random variables with the same expected value will be close to the expected value, if the number of observations is large enough.

Discussion and conclusions

Discussion of the results

Paper I showed that intention to stop smoking affected the estimated probabilities of the occurrence of consequences for both continuing and stopping smoking, whereas pregnancy did not affect the estimated probabilities. The project also concluded that health messages about smoking for all population groups should consider both future risk of mortality and immediate quality-of-life effects of smoking.

Paper II tested a model based on the product of value and belief, called expected utility (EU), on the addictive behaviour of smoking. Expected utility proved to give a good description of judgements of health consequences, and psychological and social consequences over time. Values as well as beliefs related to health consequences should be stressed in smoking cessation programmes, especially among pregnant women.

Paper III confirmed that DBP, but not SBP, reduction was associated with neurological deterioration after the intravenous administration of high-dose nimodipine after acute stroke. For low-dose nimodipine, the results were not conclusive. These results do not confirm or exclude a neuroprotective property of nimodipine. Although it was determined that inpatients treated with high-dose intravenous nimodipine led to a profound DBP reduction, any neuroprotective effect seemed to be outweighed by the hemodynamic effect.

Paper IV showed that for iron-replete patients with lymphoproliferative malignancies and cancer-associated anaemia concomitant medication, once weekly administration of subcutaneous epoetin beta and intravenous iron sucrose was markedly more effective than epoetin beta alone. Concomitant intravenous iron administration significantly increased Hb levels and the proportion of Hb responders, and produced faster Hb responses. Moreover, the weekly epoetin dose requirement was decreased by at least 25%. The study shows that intravenous iron therapy is an important consideration in the optimization of response to treatment with ESAs for cancer-related anaemia and should be considered for inclusion in clinical guidelines.

In **Paper V,** the major findings were high odds of concurrent psychoactive drug treatments, nervous symptoms and insomnia, as well as high rates of circulatory and musculoskeletal conditions in both sexes, with indicators of disability and sleep-disturbing symptoms. During a 15-year period, 35% of the men and 21% of the women who reported regular hypnotic drug treatment had also been admitted to inpatient psychiatric care. Substance abuse was diagnosed in 20% of the men and 4.3% of the women reporting hypnotic drug treatment.

In multiple logistic regression models, the highest odds for regular hypnotic drug treatment were incurred by recent/current insomnia, nervous symptoms, and other psychoactive drug treatment. The study showed that registry data is a unique resource and should be used in risk analysis within the area of medicine. Thus, the quality of the data in the databases must be discussed.

Paper VI showed that combined cardiovascular events did not differ between the treatment groups and occurred in 30.8% and 29.3% of metoprolol and verapamil treated patients respectively. Total mortality in metoprolol and verapamil treated patients was 5.4% and 6.2%, respectively. Cardiovascular mortality was 4.7% in both groups. Non-fatal cardiovascular events occurred in 26.1% and 24.3% of metoprolol and verapamil-treated patients, respectively. Psychosomatic symptoms and sleep disturbances were significantly improved in both treatment groups. The magnitudes of change were small and did not differ between treatments. Life satisfaction did not change on either drug. Withdrawals due to side effects occurred in 11.1% and 14.6%, respectively. This long term study indicates that both drugs are well tolerated and that no difference was shown in the effect on mortality, cardiovascular end points and measures of quality of life.

Paper VII showed some evidence that IgE sensitization (24%) tended to be more common among children who were seropositive against few compared with children who were seropositive against many viruses. IgE sensitization was statistically significantly less prevalent at two years of age among infants who were seropositive against EBV but not other viruses. The interaction of seropositivity against both CMV and EBV antibodies indicated a further reduction in the risk for IgE sensitization, indicating effect modification associated with seropositivity against CMV. The results indicate that acquisition of EBV infection during the first two years of life is associated with a reduced risk of IgE sensitization, and this effect is enhanced by CMV co-infection.

Conclusions and future improvements

In this thesis we have focused on risk, risk analysis and decision-making with reference to biostatistics and the field of medicine.

The thesis has showed that biostatistics and risk analysis are excellent tools to use in decision-making in the field of medicine.

In the future, it might even be possible to expand the use of high quality databases in biostatistics and risk analysis. Even though Sweden already has high quality databases, it would be beneficial to expand them. The prerequisites for monitoring public health are particularly good in Sweden thanks to several extensive national health registers of high quality, which also include personal identification numbers, unique to each citizen.

Included papers and short summaries

I.   Näsman P., Örtendahl M. (2007).
     Perceived consequences among pregnant and non-pregnant women of
     continuing or ceasing to smoke.
     International Journal of Gynecology and Obstetrics,
     Volume 99, Issue 2, pages 117-121, November 2007.

II. Näsman P., Örtendahl M. (2007).
     Values and beliefs about consequences related to smoking among
     pregnant and non-pregnant women.
     Journal of Obstetrics and Gynaecology,
     Volume 27, Issue 6, pages 558-563, August 2007.

III. Ahmed N., Näsman P., Wahlgren G. (2000).
     Effect of intravenous nimodipine on blood pressure and outcome after
     acute stroke.
     Stroke, Volume 31, Issue 6, pages 1250-1255, June 2000.

IV. Hedenus M., Birgegård G., Näsman P., Ahlberg L., Karlsson T.,
     Lauri B., Lundin J., Lärfars G., Österborg A. (2007).
     Addition of intravenous iron to epoetin beta increases hemoglobin
     response and decreases epoetin dose requirement in anemic patients
     with lymphoproliferative malignancies: a randomized multicenter study.
     Leukemia, Volume 21, Issue 4, pages 627-632, April 2007.

V.   Allgulander C., Näsman P. (1991).
     Regular hypnotic drug treatment in a sample of 32,679 Swedes:
     associations with somatic and mental health, inpatient psychiatric
     diagnoses and suicide, derived with automated record-linkage.
     Psychosomatic Medicine, Volume 53, Issue 1, pages 101-108,
     January/February 1991.

VI. Rehnqvist N., Hjemdahl P., Billing E., Björkander I., Eriksson SV.,
     Forslund L., Held C., Näsman P., Wallen NH. (1996).
     Effects of metoprolol vs. verapamil in patients with stable angina
     pectoris. The Angina Prognosis Study in Stockholm (APSIS).
     European Heart Journal, Volume 17, Number 1, pages 76-81,
     January 1996.

VII. Nilsson C., Linde A., Montgomery SM., Gustafsson L., Näsman P.,
     Blomberg MT., Lilja G. (2005).
     Does early EBV infection protect against IgE sensitization?
     The Journal of Allergy and Clinical Immunology, Volume 116, Issue 2,
     pages 438-444, August 2005.

Summary of paper I.

Näsman P., Örtendahl M. (2007).

Perceived consequences among pregnant and non-pregnant women of continuing or ceasing to smoke.

Summary

The primary objective of the study was to examine the perception of risk of smoking-related psychological and social outcomes, and the effect of pregnancy and intention to stop smoking on the perceived risk.

Eighty women were asked to make judgments about the probability of outcomes for smoking-related consequences. Four subgroups were created using the variables of pregnancy (pregnant versus not pregnant) and cessation of smoking (intention to stop versus no intention to stop). Judgments were based on the decision to stop and not stop smoking.

The study showed that intention to stop smoking affected the estimated probabilities for the occurrence of consequences for both continuing and stopping smoking, whereas pregnancy did not affect the estimated probabilities. The estimated effect of stopping smoking was statistically significant.

In conclusion health messages about smoking for all population groups should consider both future risk of mortality and immediate quality-of-life effects of smoking.

Summary of paper II.

Näsman P., Örtendahl M. (2007).

Values and beliefs about consequences related to smoking among pregnant and non-pregnant women.

Summary
The purpose of the study was to test a model based on the product of value and belief, called expected utility (EU), on the addictive behaviour of smoking. A total of 40 pregnant and 40 non-pregnant women over a period of 2 weeks performed judgments on values and beliefs about consequences related to smoking for the conditions of continuing and stopping smoking. There were no differences between pregnant and non-pregnant women in the EU of smoking.

Differences in expected utility between the conditions of continuing and stopping smoking were larger for health consequences compared with psychological and social consequences and consequences related to pregnancy.

Expected utility gives a good description of judgements over time. Values as well as beliefs related to health consequences should be stressed in smoking cessation programmes, especially among pregnant women.

Summary of paper III.

Ahmed N., Näsman P., Wahlgren G. (2000).

Effect of intravenous nimodipine on blood pressure and outcome after acute stroke.

Summary

The Intravenous Nimodipine West European Stroke Trial (INWEST) found a correlation between nimodipine-induced reduction in blood pressure (BP) and an unfavorable outcome in acute stroke. In this, our, project we sought to confirm this correlation with and without adjustment for prognostic variables and to investigate outcome in subgroups with increasing levels of BP reduction.

Patients with a clinical diagnosis of ischemic stroke (within 24 hours) were consecutively allocated to receive placebo (n=100), 1 mg/h (low-dose) nimodipine (n=101), or 2 mg/h (high-dose) nimodipine (n=94). The correlation between average BP change during the first 2 days and the outcome at day 21 was analyzed.

Two hundred sixty-five patients were included in this analysis (n=92, 93, and 80 for placebo, low dose, and high dose, respectively). Nimodipine treatment resulted in a statistically significant reduction in systolic BP (SBP) and diastolic BP (DBP) from baseline compared with placebo during the first few days. In multivariate analysis, a significant correlation between DBP reduction and worsening of the neurological score was found for the high-dose group (b=0.49, p=0.048). Patients with a DBP reduction of ≥20% in the high-dose group had a significantly increased adjusted OR for the compound outcome variable death or dependency (Barthel Index <60) (n/N=25/26, OR 10.16, 95% CI 1.02 to 101.74) and death alone (n/N=9/26, OR 4.336, 95% CI 1.131 to 16.619) compared with all placebo patients (n/N=62/92 and 14/92, respectively). There was no correlation between SBP change and outcome.

DBP, but not SBP, reduction was associated with neurological worsening after the intravenous administration of high-dose nimodipine after acute stroke. For low-dose nimodipine, the results were not conclusive. These results do not confirm or exclude a neuroprotective property of nimodipine.

Summary of paper IV.

Hedenus M., Birgegård G., Näsman P., Ahlberg L., Karlsson T., Lauri B., Lundin J., Lärfars G., Österborg A. (2007).

Addition of intravenous iron to epoetin beta increases hemoglobin response and decreases epoetin dose requirement in anemic patients with lymphoproliferative malignancies: a randomized multicenter study.

Summary
This randomized study assessed if intravenous iron improves hemoglobin (Hb) response and permits decreased epoetin dose in anemic (Hb 9–11 g/dl), transfusion-independent patients with stainable iron in the bone marrow and lymphoproliferative malignancies not receiving chemotherapy. Patients (n=67) were randomized to subcutaneous epoetin beta 30000 IU once weekly for 16 weeks with or without concomitant intravenous iron supplementation. There was a significantly ($p<0.05$) greater increase in mean Hb from week 8 onwards in the iron group and the percentage of patients with Hb increase ≥2 g/dl was significantly higher in the iron group (93%) than in the no-iron group (53%) (per-protocol population; $p=0.001$).

Higher serum ferritin and transferrin saturation in the iron group indicated that iron availability accounted for the Hb response difference. The mean weekly patient epoetin dose was significantly lower after 13 weeks of therapy ($p=0.029$) and after 15 weeks approximately 10000 IU (>25%) lower in the iron group, as was the total epoetin dose ($p=0.051$).

In conclusion, the Hb increase and response rate were significantly greater with the addition of intravenous iron to epoetin treatment in iron-replete patients and a lower dose of epoetin was required.

Summary of paper V.

Allgulander C., Näsman P. (1991).

Regular hypnotic drug treatment in a sample of 32,679 Swedes: associations with somatic and mental health, inpatient psychiatric diagnoses and suicide, derived with automated record-linkage.

Summary
In the project we studied Swedish survey responders who reported regular treatment with hypnotic drugs, to find associations to perceived health problems, inpatient psychiatric diagnoses, and subsequent suicide. Among 32,679 sampled Swedes, 26,952 (83%) participated, 500 of which (2%) reported regular hypnotic drug treatment. The rate of treatment was higher in women, and increased by age in both sexes.

The major findings were high odds of concurrent psychoactive drug treatments, nervous symptoms and insomnia, as well as high rates of circulatory and musculoskeletal conditions in both sexes, with indicators of disability and sleep-disturbing symptoms. During a 15-year period, 35% of the men and 21% of the women who reported regular hypnotic drug treatment had also been admitted to inpatient psychiatric care. Substance abuse was diagnosed in 20% of the men and 4.3% of the women reporting hypnotic drug treatment. In multiple logistic regression models, the highest odds for regular hypnotic drug treatment were incurred by recent/current insomnia, nervous symptoms, and other psychoactive drug treatment.

The project concluded that therapy was principally given according to some current peer guidelines. However, further research is needed into the risk/benefit ratio of sustained hypnotic drug therapy in patients with qualifying somatic and psychiatric disorders to obtain a more uniformly based consensus.

Summary of paper VI.

Rehnqvist N., Hjemdahl P., Billing E., Björkander I., Eriksson S. V., Forslund L., Held C., Näsman P., and Wallén N. H. (1996).

Effects of metoprolol vs. verapamil in patients with stable angina pectoris: The Angina Prognosis Study in Stockholm (APSIS)

Summary
The objective of the study was to study long-term treatment effects of metoprolol or verapamil on combined cardiovascular end points and psychological variables in patients with stable angina pectoris.

The study was a randomized, double-blind, double-dummy trial and included 809 patients under 70 years of age with stable angina pectoris. The mean age of the patients was 59 ± 7 years and 31% were women. Exclusion criteria were myocardial infarction within the previous 3 years and contraindications to beta-blockers and calcium antagonists. The patients were followed between 6 and 75 months (median 3.4 years and a total of 2887 patient years). The patients were treated with either metoprolol (Seloken ZOC 200 mg o.d.) or verapamil (Isoptin Retard 240 b.i.d.). Acetylsalicylic acid, ACE inhibitors, lipid lowering drugs and long acting nitrates were allowed in the study. The end points were: death, non-fatal cardiovascular events including acute myocardial infarction, incapacitating or unstable angina, cerebrovascular or peripheral vascular events. Psychological variables reflecting quality of life i.e. psychosomatic symptoms, sleep disturbances and an evaluation of overall life satisfaction.

The result of the study showed that combined cardiovascular events did not differ and occurred in 30.8% and 29.3% of metoprolol and verapamil treated patients respectively. Total mortality in metoprolol and verapamil treated patients was 5.4% and 6.2%, respectively. Cardiovascular mortality was 4.7% in both groups. Non-fatal cardiovascular events occurred in 26.1% and 24.3% of metoprolol and verapamil-treated patients, respectively. Psychosomatic symptoms and sleep disturbances were significantly improved in both treatment groups. The magnitudes of change were small and did not differ

between treatments. Life satisfaction did not change on either drug. Withdrawals due to side effects occurred in 11.1% and 14.6%, respectively.

This long term study indicates that both drugs are well tolerated and that no difference was shown on the effect on mortality, cardiovascular end points and measures of quality of life.

Summary of paper VII.

Nilsson C., Linde A., Montgomery SM., Gustafsson L., Näsman P., Blomberg MT., Lilja G. (2005).

Does early EBV infection protect against IgE sensitization?

Summary
There is indirect evidence that an increased infectious burden is associated with a decreased prevalence of IgE-mediated allergy during childhood. The objective of the study was to determine whether there is a relation between the serostatus of 13 different viruses and parentally reported infections and IgE sensitization in 2-year-old children. We also wanted to investigate whether there is an interaction between cytomegalovirus (CMV) and Epstein-Barr virus (EBV) in relation to IgE sensitization.

A total of 246 infants were followed prospectively to 2 years of age with clinical examinations, skin prick test, and specific IgE analyses and through analysis of seropositivity against adenovirus, influenza, parainfluenza, respiratory syncytial virus, CMV, EBV, herpes simplex virus, human herpes virus 6, and varicella-zoster virus.

There was some evidence that IgE sensitization (24%) tended to be more common among children who were seropositive against few compared with children who were seropositive against many viruses, but this was not statistically significant, and there was no consistent trend across the groups. IgE sensitization was statistically significantly less prevalent at 2 years of age among infants who were seropositive against EBV but not other viruses (adjusted odds ratio, 0.34; 95% CI, 0.14-0.86). The interaction of seropositivity against both CMV and EBV antibodies indicated a further reduction in the risk for IgE sensitization (adjusted odds ratio for interaction, 0.10; 95% CI, 0.01-0.92), indicating effect modification associated with seropositivity against CMV.

Our results indicate that acquisition of EBV infection during the first 2 years of life is associated with a reduced risk of IgE sensitization, and this effect is enhanced by CMV co-infection.

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