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Adherence to drug treatment and interpretation of treatment effects

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Abstract
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Suboptimal adherence to medical treatments is prevalent across several clinical conditions and can lead to treatment failure. Adherence is a far from fully explored phenomenon and there is little knowledge about how patients interpret treatment effects. Commonly used treatment evaluation measures are often relative measures, which may be difficult for lay people and patients to understand.

The overall aim of this thesis was to investigate factors with relevance to adherence, to estimate treatment effects with the time-based Delay of Event (DoE) measure in anticoagulant preventive treatments, and to explore how lay people responded to the DoE measure, as compared with established measures, regarding treatment decisions and effect interpretation.

A quantitative population-based cross-sectional design was used for Study I. Study II used data from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) clinical trial and estimated effects as DoEs. Studies III and IV were carried out as randomised survey experiments.

The results showed that general adherence behaviour was associated with both environmental and social factors. Estimations of DoE showed that stroke or systemic embolism was delayed 181 (95% CI 76 to 287) days through twenty-two months of apixaban use, as compared with warfarin use. The delay of major and intracranial bleeding was 206 (95% CI 130 to 281) and 392 (95% CI 249 to 535) days, respectively, due to apixaban use for twenty-two months, as compared with warfarin use. Presenting preventive treatment effects as DoEs to lay people was associated with high willingness to initiate treatment and positive views on treatment benefits and willingness to pay for treatment.

Non-optimal adherence was partly associated with modifiable factors and it might be possible to increase adherence by managing these factors. Estimations of DoEs in preventive treatments gave information on effects regarding delay of different outcomes; the estimation also provides tools that might be useful for interpreting and communicating treatment effects in clinical decision-making. Lay people seemed to react rationally to variations in DoE magnitude; a higher proportion accepted treatment when the magnitude was greater.

Keywords: Medication adherence, Health-seeking behaviour, Chronic treatment, Cardiovascular treatments, Anticoagulants/therapeutic use, Treatment outcome, Effect measure, Quality of care, Medical decision-making, Necessity-concern framework, Choice behaviour, Risk communication, Risk perception, Health communication

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långvariga läkemedelsbehandlingar*

Att tänka stort är störst

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Berglund, E., Westerling, R., Lytsy, P. Living environment, social support and informal caregiving are associated with health care seeking behaviour and adherence to medication treatment: a cross-sectional population study. *Accepted for publication in Health & Social Care in the Community.*

II Berglund, E., Wallentin, L., Oldgren, J., Renlund, H., Hylek, E. M., Lopes, R. D., McMurray, J. J. V., Lytsy, P. Effects of apixaban compared with warfarin as gain in event-free time – an novel assessment of the results of the ARISTOTLE trial. *In manuscript.*

III Berglund, E., Westerling, R., Sundström, J., Lytsy, P. (2016) Treatment effect expressed as the novel Delay of Event measure is associated with high willingness to initiate preventive treatment - A randomized survey experiment comparing effect measures. *Patient Education and Counseling,* 99(12):2005-2011.

IV Berglund, E., Westerling, R., Sundström, J., Lytsy, P. (2018) Length of time periods in treatment effect descriptions and willingness to initiate preventive therapy: A randomised survey experiment. *BMC Medical Informatics and Decision Making.* 18(1):106.

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Contents

Abbreviations

4S	Scandinavian Simvastatin Survival Study
AF	Atrial fibrillation
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial
ARR	Absolute risk reduction
BMQ/-S	Beliefs about Medicines Questionnaire/Specific
$CHADS_2$	Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke/transient ischemic attack
CHA_2DS_2-VASc	Congestive Heart failure, hypertension, Age, Diabetes, Stroke, Vascular disease, Age and Sex
CI	Confidence interval
CVD	Cardiovascular disease
CVM	Contingent valuation method
cTTR	centre's average time in therapeutic range
DoE	Delay of Event
HR	Hazard ratio
HSB	Health-seeking behaviour
INR	International normalised ratio
LDL	Low-density lipoprotein
MDM	Medical decision-making
MI	Myocardial infarction
NCF	Necessity-Concern Framework
NNT	Numbers needed to treat
NOAC	Non-vitamin K antagonist oral anticoagulants
OR	Odds ratio
PLATO	Platelet Inhibition and Patient Outcomes trial
RCT	Randomised controlled trial
RRR	Relative risk reduction
SCORE	The Systematic COronary Risk Evaluation
SDM	Shared decision-making
SRM	Self-regulatory model
VKA	Vitamin K antagonist
WTP	Willingness to pay

Prologue

One of the major concerns in medical science is determining if, how, and why a factor or treatment is related to an outcome. This is a challenge in regard to determining causality and when estimating the magnitude of an effect, and further in communication and implementation of health policy and guidelines. There is an ongoing discussion on how this process should be carried out and what methods, measurements, and formats are most advantageous for effect estimation, interpretation, and communication.

While the concept of *time* is a very abstract phenomenon, *time periods* are of simpler nature for humans to understand. A thrilling thought is to use the dimension of time periods, to estimate, interpret, and communicate treatment effects. In this thesis, I have had the opportunity to deal with this matter. However, the journey that led to this research began with other problems evident in today's health care; preventive treatment may decrease the burden of disease, yet adherence to such treatments is low in general and there is little knowledge on how people interpret preventive treatment benefits. In the effort to understand patient behaviours regarding treatments, the light of curiosity led back to the source of knowledge and how an effect is estimated, and further to the question of which effect measures that might serve as useful in clinical decision-making regarding treatments. Together with supervisors and colleagues, it has been possible to both increase the knowledge regarding adherence, elaborate novel time-based measures, and study people's reception of time-based measures. This thesis is also organised in accordance with this chronology: it starts with adherence and health-seeking behaviours and associated factors; the next part consists of an effect estimation where the effect of different anticoagulant drugs have been investigated and presented as delay of events; the last two studies evaluated how lay people responded to, firstly, different effect formats, and secondly, how variations in a time-based effect measure affected views and willingness to take a prescribed medication.

The goal with this thesis has been to increase knowledge regarding treatment adherence and to develop strategies that could be used to increase a patient's understanding of proposed treatments, and potentially increase adherence. It is now time for me to leave this work with you, the reader, and I do that with the hope that its contents will improve your understanding of adherence and the possibilities with using different effect measures in research and health care.

Introduction

Medical treatments need to be used correctly to be effective. Medication usage and adherence to prescribed treatments depends on the behaviour of the medicated individuals and has an impact on people's health, as do other behaviours, such as eating, physical activity, health-seeking, and more [1]. Since drug therapies depend on patients' behaviours for successful results, non-optimal usage of preventive cardiovascular treatments is considered a risk factor in reaching treatment goals [2], causing increased morbidity [3-5], and mortality [6, 7]. Suboptimal adherence is a problem evident in both curative, symptom-reductive and preventive treatments, and is often considered and managed as a public health concern [1, 8].

Preventive treatments or prophylaxes aim to prevent diseases before they occur, by reducing the risk of disease events and delay the occurrence of symptomatic events. In some cases, prevention may completely avert disease occurrence, but in most chronic diseases, such as cardiovascular disease, it is more likely to postpone disease events [9, 10].

Preventive treatments can be used in a primary setting, which is before any symptoms or manifest diseases have developed. They can also be used in a secondary (manifest disease) setting, where known manifestations and symptoms are already present. While preventive treatments typically offer no manifest benefits to their users, as they rarely experience any symptoms that are reduced by the treatments, the potential outcome benefits are in the patients' future.

Cardiovascular diseases and preventive treatments

Among the most common chronic diseases in the western world are those affecting the circulatory system and its organs, cardiovascular diseases (CVD), which are also among the most common causes of death [11]. Together with diabetes mellitus, cancer, and lung disease, which are all non-communicable diseases, CVD are the leading causes of death globally [12]. CVD is a broad class of disorders involving the heart or blood vessels, and includes diseases such as angina, myocardial infarction (MI), stroke, heart failure, hypertension, and thromboembolic disease, among others.

Ischemic heart disease, or coronary artery disease, is a disease characterized by reduced blood flow to the heart muscle, and has there are a number

of known risk factors, both modifiable and non-modifiable. Dyslipidaemia, i.e., abnormal levels of blood lipids, is estimated to contribute to the development of several cerebrovascular diseases, such as atherosclerosis, MI, and stroke, as well as mortality [13-15]. A lowering of low-density lipoprotein cholesterol (LDL) is often the primary target of treatments aimed at reducing the risk of CVD. Several studies have demonstrated benefits of statins (hydroxymethylglutaryl-CoA reductase inhibitors) to achieve reductions in LDL cholesterol, CVD events, and cardiovascular and all-cause mortality [16-20], and increase in high-density lipoprotein cholesterol [21].

Hypertension or high blood pressure increases the workload of the heart and blood vessels, and will over time increase the risk of CVD. Medications such as beta-blockers, angiotensin-converting-enzyme inhibitors, diuretics, and others are used to reduce blood pressure and thereby lower the risk of CVD [22, 23].

Thromboembolism is when a blood clot inside a blood vessel blocks the blood flow through the circulatory system, increasing the risk of embolism and stroke [24]. Venous thromboembolism is usually managed with antiplatelet drugs, which are a type of antithrombotic drug [25, 26].

A common heart rhythm disorder is atrial fibrillation (AF), an irregular heart rhythm associated with increased risk of stroke, heart failure, and premature mortality [27]. AF can increase the risk of blood clots forming in the heart, which may then circulate to other organs and lead to blocked blood flow. If this occurs within the brain, it may lead to ischemic stroke. Among patients with AF, vitamin K antagonist (VKA) anticoagulants such as warfarin, and novel Non-vitamin K antagonist oral anticoagulant (NOAC) agents are preventive and reduce the risk of stroke and mortality [28] [29, 30].

Heart failure often follows another CVD condition, such as one or more MI, high blood pressure, or AF [31]. Different antihypertensive drugs, such as angiotensin-converting enzyme inhibitor, angiotensin receptor blockers and digoxin, are used in treatment regimens [32].

People with increased risk of CVD typically receive combinations of drug therapies to lower this risk. Several lifestyle modifications are also of importance in lowering the risk of CVD, targeting the domains of diet, physical activity, and smoking habits.

Several methods, guidelines, and tools have been developed to assess the risks of CVD and provide guidance on when a drug treatment is recommended. The commonly used Framingham score and the Systematic COronary Risk Evaluation (SCORE) are recommended for assessing CVD risk regarding MI and stroke [33]. The SCORE project developed a system of risk estimation for clinical practice in Europe, where the 10-year risk of fatal CVD is estimated based on an individual's sex, age, smoking status, total cholesterol, and systolic blood pressure [34]. Thresholds for intensified risk factor management (mostly with drugs) are when the risk of a CVD event is increased: in the Framingham score when a patient has 20% or higher risk of

CVD, and in SCORE if a patient has a risk of 5% or higher and increased LDL cholesterol levels [35, 36].

In AF patients, the risk of stroke is assessed with the Congestive heart failure, Hypertension, Age > 75, Diabetes, prior Stroke/transient ischemic attack (CHADS$_2$) score. In the CHADS$_2$ score, the presence of congestive heart failure, hypertension, age 75 years or older, or diabetes mellitus adds one point, and two points are added for history of stroke or transient ischemic attack [37]. The later Congestive heart failure, hypertension, age, diabetes, stroke, vascular disease, and Sex (CHA$_2$DS$_2$-VASc) score incorporating additional risk factors for estimating the risk of stroke in AF patients [38]. Both the CHADS$_2$ and CHA$_2$DS$_2$-VASc have predictive value for outcomes in AF patients and are used for evaluating if anticoagulation therapy is required, thus the CHA$_2$DS$_2$-VASc classification method extends validity and may improve the prediction of stroke and therapeutic decision-making [39].

Health care use and health-seeking behaviour

Preventive interventions, such as drug treatments for CVD, primarily depend on people's utilization of health care services. A major component affecting health care utilization is people's health-seeking behaviour (HSB). HSB is broadly defined as activities performed by individuals who perceive themselves as having a health problem or being ill, with the purpose of finding an appropriate remedy [40]. A non-optimal HSB occurs when a person refrains from/avoids seeking care entirely or does not seek care in accordance with his or her expected needs [41]. HSB are, together with other factors such as socioeconomics and behaviour of health care providers, critical for access to health care services, which is a determinant of health [42-45].

There are differences in how people and groups of people seek care. Socially vulnerable groups more often than their less vulnerable counterparts refrain from seeking care or do not seek care in accordance with their expected needs [46]. Factors associated with HSB and health care utilization include economy/availability [47], gender [48], being foreign-born [48], education level [48], and lack of confidence in medical services [48].

Adherence and non-adherence to preventive treatment

People's use of treatments and drugs and related behaviours have been of major interest since it became evident that adherence to treatment is a key link between health care and outcome [1, 49]. Different terms have been used throughout history to describe this phenomenon, such as: doctor's orders, compliance, concordance, and adherence [50, 51]. Some of these terms have been used interchangeably, although their meanings differ somewhat

and they should not be considered synonymous. Doctor's orders and compliance were early terms, but have been criticised for picturing an authoritarian and controlling situation by the physician. Adherence is a term more often used today, it is defined as: "the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a health care provider" [51]. Furthermore, lack of adherence to treatment is defined as: "when a patient is not taking their medication at prescribed intervals or during the entire period, as recommended by a health care provider."

Two types of non-adherence can be identified: underuse and overuse of medication. In regard to CVD treatments, underuse is a major problem [52, 53]. Adherence to a drug treatment is often divided into primary and secondary adherence [1]. Primary adherence involves a patient redeeming a prescribed medication (picking up/buying the prescription drug at a pharmacy). Secondary adherence requires the patient to take the medication as prescribed.

Long-term adherence to the pharmacological treatments of chronic diseases has been estimated to an average of around 50% [51, 54], and a number of theories have been suggested to explain why adherence is inadequate. Factors with known association to adherence include demographics [55-58], a patient's understanding and perception of medication [51, 59], sickness- and treatment-related factors [60-63], side effects [59], health locus of control [59, 64], being an informal caregiver (provide unpaid assistance to a person with illness or disability) [65], and health literacy [66-69]. Health literacy is defined as a patient's ability to obtain, process, communicate, and understand basic health information and services needed to make appropriate health decisions [70].

HSB is sometimes associated with adherence and shares similar risk factors in some cases [71, 72]. There is also a chronological relationship between HSB and adherence: a patient must first seek care, or come in contact with health care in some other way, to obtain prescriptions for drugs. Therefore, optimal health care is dependent on both HSB and adherence.

In addition to individual factors, research regarding non-adherence and failures to follow treatment plans often embrace the health care organization and factors such as poor access to health care/drug supplies, unclear information about drug administration, as well as poor follow-up and poor provider-patient communication and relationships [73]. To improve treatment outcomes it is critical to identify key determinants of access to medication, HSB, and non-adherence [74], and find strategies to modify factors of importance.

Adherence-enhancing methods and communication

Several interventions have been carried out over the years, aimed at increasing adherence to various treatments. Effective interventions to improve adherence to long-term treatments often seem to be multifactorial and encompass several components. Typically, adherence interventions include components such as information, communication, counselling, decision aid, (extended) convenient care, reminders, reinforcement, telephone follow-up, self-monitoring, family therapy, crisis intervention, supportive care, and additional supervision or attention [1, 75-77]. Therapeutic methods such as motivational interviewing [78, 79], and educational and behavioural therapy interventions are also used in adherence interventions [80, 81].

In chronic diseases when patients, and sometimes family caregivers, are in a control of large parts of the care domains, self-management is important [82]. Self-management incorporates multiple concepts, such as self-care, self-monitoring, and adherence to treatment. Self-management interventions often relate to problem-solving and health behaviour changes for maintaining long-term benefits; in practice, this could be provision of information and support, strengthening coping skills and empowerment [83, 84].

Adherence and associated health behaviours, such as HSB, relate to the patient in the health care organization, and therefore the context, approach, and communication used within health care are important [73, 79]. Several studies indicate that improved health communication quality between health care providers and patients may result in better adherence [56, 73, 85].

Health communication is about the communication strategies that are used to inform and influence individual decisions that enhance health, and includes information about risks and treatments options [86]. Health communication is both past- and future-orientated; it can include information regarding historic factors associated with a present health condition, and a forecast of a patient's health status and how it may be modified with different actions. The goal is to facilitate informed choices with the support of evidence-based medicine and to enable patients to make advantageous choices.

Communication about health risks and treatment effects often includes the estimation of risks in relative numbers, which may lead to misunderstandings due to low numeracy and statistical illiteracy among people [87-90]. Statistical literacy is the ability to understand and critically evaluate the statistical results that permeate our daily lives [91]. Both patients and health care professionals have difficulties in understand statistics and the meaning of certain numbers. The general shortcomings in statistical literacy cause misunderstandings that may render the goal of "informing" in health communication and informed decisions [90].

The research proposes that the problem with statistical illiteracy could be managed by changing the representation and communication of numbers in

health care. By communicating absolute rather, than relative measures, using frequentist formulations, instead of single event probabilities, and using natural frequencies instead of probabilities, insight regarding risk information might be more easily achieved in health communication [90].

Theoretical framework and models

The theoretical part of the thesis focuses on health behaviour, adherence, medical decision-making, risk perception, and measures of treatment effect. Central theoretical frameworks are theories and models that relate to adherence and how treatment effects can be estimated and interpreted.

Context, health and health behaviour

The environment and the context that people live in have implications for health [92], which has been broadly acknowledged since the Lalonde report [93]. The environment is usually classified based on environmental size, such as micro and macro environmental level, or environmental type [94]. Another way to classify environments is into dimensions, such as social and physical environment [95].

The physical environment includes housing, infrastructure, parks, streets, and other physical structures. The physical environment is known to affect health and well-being [95-98], and is important for health-related behaviours such as mobility and physical activity.

The social environment is the environment created by the people living in the neighbourhood [95]. The social environment may affect public health in several ways; exposure to violence in an area directly affects health through injuries from attacks; perceived safety also affects stress levels [99], and behaviours such as physical activity [100]. The social environment includes different levels of trust and efficacy [101], which can act as a buffer against stressors [102]. The social environment and neighbourhood related factors have been associated with health outcomes such as psychological distress, depression, wellbeing, and overall health [103-108]. Another aspect is what a community offers in terms of access to (common) resources, such as jobs, (qualitative) schools, hospitals, public transport, infrastructure, and facilities. Accumulation of negative exposures, affecting people living in socioeconomically weak areas, is likely to impact health negatively [109-111]. Community socioeconomic context is seen as a contributor to health status, independent of individual factors [92, 95, 112, 113].

Living environments includes any aspects of the environment that humans live in, and encompasses both indoor (including homes, residences, workplaces, and vehicles) and outdoor environments (including neighbourhoods,

infrastructure, streets, and land use). Several studies have found associations between the living environment, and chronic diseases such as cardiovascular diseases [114-118], and diabetes [119, 120]. The local environment has been shown to be associated with known risk factors for cardiovascular disease such as smoking, systolic blood pressure, and serum cholesterol [121, 122]. The local environment has also been associated with health-related behaviours [123-126], and use of anxiolytic-hypnotic drug has been linked to social context [127].

Models regarding health-seeking behaviour

A person's social and socioeconomic situation is known to impact health and health service use in several ways [46]. Social support refers to the resources provided by others that facilitate an individual's achievement of a goal and is usually divided into instrumental and emotional [128]. Social support is known to impact health and health-related behaviour and has associations to health behaviour and adherence, as do other social factors [73].

One of the most widely spread theories regarding health care utilization is based in the two concepts of "need components" and "provider factors" [129]. "Need components" refers to perceived needs and how they are transformed into demands due to an inclination to seek medical care. The concept of "provider factors" refers to how providers are brought into line with patients' needs and resources.

Andersen's Behavioural Model of Health Services Use was developed by Ronald M. Andersen in 1968 and has been further developed since [130]. In its original form, the model aimed to explain the use of health services based on predisposing characteristics, enabling resources, and needs.

There are also other models used for social and environmental determinants of health, such as the main determinants of health model by Dahlgren and Whitehead sometimes called the "rainbow model" [131]. In the model, the individuals are placed at the centre where they are surrounded with various layers with influences on health. The model outlines that the lifestyle and health behaviour is affected by the environment, health care, etcetera. In addition, a similar concept is outlined in the multilevel approach to epidemiology [132].

Models regarding adherence

There are individual differences in health behaviour that may depend on psychological or cognitive variables, and social cognitive variables have been used to analyse differences in several health behaviours [133].

Social cognition models that have been used in studies concerning treatment adherence include: the Health Belief Model [134, 135], the Transtheoretical Model [136], the Protection Motivation Theory [137, 138], and the Self-Regulatory Model (SRM) [139, 140]. These models have both similarities and differences. The SRM model proposes that a health-related behaviour is a cognitive response influenced by a patient's perception of and emotional response to treatment. These responses can be derived from both manifest symptoms and concerns about a health threat, or an experience or concern about the side effects of a treatment. Research shows that the adherence behaviour may be the result of a decision on the part of the patient and identifies some of the beliefs relevant to these decisions. There are also adherence decision models that use a cost-benefit analysis, in which the benefits of treatment are weighed against a perceived barrier [141].

The Necessity-Concern Framework (NCF) was developed specifically to investigate drug assessment, treatment adherence, and what types of specific beliefs were associated with adherence [142]. According to the NCF, a patient's decision and behaviour regarding adherence is the result of a trade-off between the patient's perceived need for a prescribed treatment (necessity) and their worries about the adverse effects that may result (concern). In this framework, cognitive representations of treatment consist of risk determination and risk evaluation [143], with both aspects being further subdivided.

Risk determination consists of risk identification and risk estimation, where risk estimation includes an assessment of the probability of occurrence as well as the magnitude of the consequences. Risk evaluation is made up of risk aversion and risk acceptance.

This type of dividing and weighing aspects of an alternative as pros and cons (from the Latin expression "pro et contra") is also the basis for old theories describing general decision-making. For medical purposes, there are several models that use a type of balancing between advantages and disadvantages to describe decision-making and patient behaviour. The hypothesis is that patients weigh positive and negative perceptions of treatment or health advice, and the weight balance they perceive directs their decisions and behaviours. The theory have been used in time trade-off models with quality-adjusted life years [144], and in anticoagulation therapy in AF patients [145].

Through the Beliefs about Medicines Questionnaire (BMQ), the NCF has been operationalised into a practical measurement with separate subscales for the necessity and concern dimensions. Several studies have used the NCF to study adherence to different treatments [146]. In 2012, a conceptual model of balanced adherence influenced by treatment and locus of control factors was constructed to examine the relationships and structure between beliefs about CVD treatments, adherence and other factors among statin users [59], see Figure 1.
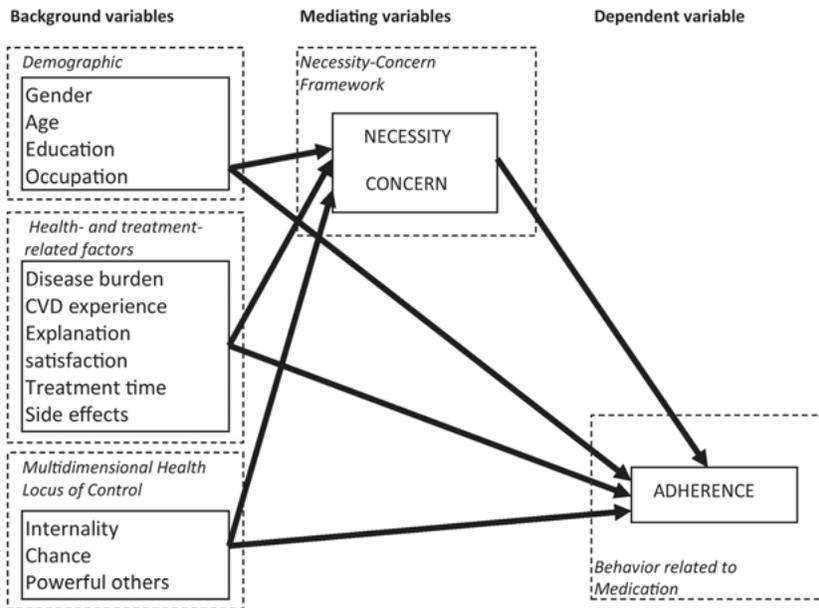
Figure 1. Model of balanced adherence influenced by treatment and locus of control factors [59].

Analysis of empirical data on statin users using this model showed that patients who reported high perceptions of necessity of treatment seemed to be more adherent [59]. Disease burden, cardiovascular disease experience, and high locus of control regarding powerful others were associated with a higher perception of necessity of treatment. High satisfaction with the treatment explanation was associated with a higher perception of necessity of treatment and lower concern about treatment. Experiencing side effects appeared to increase concern about treatment and lower adherence. The model have been used in other settings regarding adherence to antihypertensive drugs, and similar results were found [147].

Medical decision-making

Decision-making is a key activity in health care, and medical decision-making (MDM) has developed into a broad field including decision-making and informatics applied on medical and health care concerns. Research in MDM has developed into a both descriptive and normative discipline. The descriptive discipline has the goal of explaining how patients and health care professionals make decisions and identify barriers to, and facilitators of, effective decision-making. The normative and prescriptive discipline endeavours to propose standards for ideal decision-making and seeks to devel-

op tools and methods that can facilitate for patients, health care professionals, and policymakers in making desirable decisions [148].

Like any decision-making, MDM follows the process of identifying and choosing alternatives based on the values, preferences, and beliefs of the decision-maker. People (and groups) use different decision-making techniques when handling situations that call for a decision. Some decision-making techniques are more structured, such as balancing between pros and cons (see the section above for example), while others are less so, such as flipping a coin [149]. There have been debates concerning biases that influence judgment and affect decision-making processes. Biases relevant to medical judgment and decision-making that can compromise results and cause diagnostic errors can occur at the individual level, for instance as a failure of decision-making shortcuts (heuristics), or at the structural level [150, 151].

MDM needs to be dealt with under different circumstances and in different contexts. Medical decisions are rarely made in complete certainty; instead they are made in different risk scenarios and with various degrees of uncertainty. It is common to distinguish between decisions made [152]:

- Under certainty; a situation where alternatives are identified and the outcome of each alternative is known with (reasonable) certainty.
- Under risk; a situation where an alternative's outcome cannot be predicted with certainty, but there is enough information to predict the probability of the outcome.
- Under uncertainty; a situation where the probabilities of different alternatives and/or possible outcomes are unknown.

To reduce uncertainties, health care uses science and clinical trials in the pursuit of evidence regarding treatments, to facilitate informed decision-making in clinical practice [153]. Results from trials regarding the effects of preventive drugs most often show the probabilities of developing a specific disease (outcome) for the compared groups and, thus enable presentation of the effects of a risk-lowering drug. The risk figure is typically based on the proportion of a (study) population that develops a specific outcome, and the preventive effect is assessed by comparing outcomes in a treated group and a control (e.g., non-treated or other control condition) group. However, even when the probabilities are unveiled through studies, the strength of the association between a specific outcome and a preventive treatment can be less than clear and difficult to assess. Also, the outcome is not always known to its full extent; diseases may have different expressions, prognosis, onsets, etc. in different patients, because of their additional and unique combination of risk factors. Another problem is when a group measure from a study, such as an average, is transferred and applied to an individual patient, which is often necessary in the clinical practice. Altogether, even when using accurate

health information and clinical results, MDM is usually associated with both uncertainties and risks.

Several models and methods of clinical decision-making are discussed in the literature, within these models patients and health care professionals assuming different roles in the medical consultation process. Prominent among these are the paternalistic, informed, professional-as-agent, consumerist, and shared model [154, 155]. The major differences between these models are the extents of involvement on the part of the patient and the health care provider, respectively. The models may be sorted in a spectrum, where on the one side the physician assumes the responsibility of the clinical decision with very little joint deliberation with the patient, and, on the other side, the clinical decision is made by the patient by himself after obtaining medical information that could enable him/her to make an appropriate decision.

The shared decision-making (SDM) approach is somewhere at the middle of this spectrum, with patients and physicians exchanging information, discussing the details of the medical problems, exploring available treatment options, and settling on a treatment plan together [156, 157]. The SDM is about fostering patient involvement in medical decisions and an often mentioned hallmark for SDM is that patients and providers have different – but equally valuable – perspectives and roles in the medical encounter. Moreover, SDM is suggested to include several key characteristics, such as: that at least two parties are involved; that parties share information; that parties take steps to build a consensus about the preferred treatment, and that an agreement is reached on the treatment to implement [154]. A related concept is "shared accountability" in which all stakeholders within the health care system, including the patient, are responsible for the care process and outcomes [158]. SDM is often referred to as overlapping with, or be a part of, patient- and person-centred care [159, 160], and is frequently advocated in teaching and research [156, 157].

Risk assessment and risk perception

If the outcome of a medical treatment cannot be known with full certainty, patients and health care professionals need to make choices and deal with decisions that involve risk. Risk and hazard describe the relationship between: a risk source (e.g., activity, condition, or agent) and an event (e.g., disease). There is a difference between the two terms, hazard and risk; while a hazard is something that has the possibility to cause harm, a risk is the likelihood, e.g., high or low, that a hazard will actually cause harm. Another important term is exposure; which represents the extent to which a risk source reaches an object, e.g., a human [161]. Medical risks are most often assessed thorough statistical figures, showing the probability that one cir-

cumstance leads to a specified negative event. These measures are normally considered objective figures. On the other hand, risk perception, how risks are perceived by individuals, is understood in a more subjective and emotional way [162].

People have different attitudes towards risk and risk aversion [163]. Several individual characteristics and context may influence how a certain risk is perceived [164, 165]. There is a range of emotions which impact on risk perception [166], such as dread, worry, and fear [167]. People may also be sensitive to risk framing. and make decisions depending on how the options are presented which is a cognitive bias called the framing effect [168]. However, risk is a part of life and both under- and overestimation of risks having potential for unfortunate consequences [169].

Choices regarding treatment options involve a comparison of the desirability of alternative medical treatments, and the probability of getting the desired outcome. Each choice of a medical treatment may be characterised as a (risky) option with a set of possible outcomes and associated probabilities. A central theory is that rational decision-makers will, when presented with a choice, take the action with the greatest expected utility [170]. Expected utility is the expected value produced by an action, e.g., a treatment, and represents the sum of utility of each of its possible consequences, individually weighted by their respective probability of occurrence. Expected utility theory is considered a normative model of decision-making; however, the assumption that decision-makers follow rational normative assumptions has been widely criticised [166].

MDM concerning preventive treatment contains both the element of risk and uncertainty, which needs to be considered in health care management when evaluating the benefit (and potential harm) of a specific treatment, as well as in risk communication to patients. Health information affects people differently and gives rise to different emotions, which also affects responses in individuals, including their perception of risk [171]. Studies have demonstrated that the format chosen for health information, especially treatment descriptions and risk reductions in regard to chosen endpoints, affects decision-making [172-181].

Effect measures and treatment description

Treatment effect measures are used to assess whether an intervention has an effect and the effect size, but may also be used to inform individuals about the advantages (or disadvantages) of a treatment. Regarding preventive medical treatments, effects are preferably estimated in randomised controlled trials (RCTs), where a treatment group is compared with a control group (that did not receive the drug, a placebo, or a "gold" standard treatment). The randomization is usually seen as an effective method to distribute potential

confounders in a random way between groups, thus, differences in outcomes at the end of a study period may be attributed to the experimental factor: the treatment. Outcomes can be assessed on different scales, as continuous, categorical, or dichotomous types of variables, and using various different sorts and scoring. In many RCTs, the major outcome is dichotomous/binary, i.e., the outcome of interest occurs or not.

The established effect measures typically relate the proportions of events in compared groups, thus comparing proportions that have developed a certain event in the treatment group vs. the control group. There are several ways to summarise the effects in statistical terms [182]. Well-established measures to describe effects include natural numbers, absolute or relative frequencies and proportions in compared groups, relative risk reductions (RRRs), and absolute risk reductions (ARRs), numbers needed to treat (NNT), odds ratios (ORs), and hazard ratios (HRs). There are also graphical/visual information tools such as survival or mortality curves [183], and measures that provide a population perspective, such as the disease impact number and the population impact number [184]. A treatment may also cause harm, and variants of the RRR, ARR, and NNT are used for treatment harm measures, such as relative risk increase, absolute risk increase, and number needed to harm [185].

Different measures convey somewhat different perspectives of a treatment effect [186]. The relative measures, such as RRR, have the advantage of depicting the average risk lowering effect and being stable across populations with different baseline risks. However, they have the major disadvantage of not reflecting the baseline risk of the individuals with regard to the outcome being measured, as RRR does not take into account the individuals' risk of achieving the intended outcome without the intervention. The absolute risk measures, such as ARR, overcome these drawbacks because they reflect the baseline risk and portray the effect at the population level, i.e., the percentage of the population that will benefit from the treatment.

Established effect measures can be hard to understand for several reasons, one being that health care professionals, patients, and people in general find it difficult to understand statistics and statistical reasoning [87, 89, 187]. These difficulties regarding understanding of effects and evidence are problematic in clinical practice and health care, where research-based evidence is implemented, often translated into guidelines providing the basis for decision-making [188, 189]. Alternative methods and measures have been suggested to complement established ones to estimate treatment effects and to be used in MDM; those include time-based measures [190, 191].

Time-based treatment effect measures

Several types of time-based figures have been used to describe treatment effects, such as event-/disease-free time, survival time, postponement or

time-to-event/relapse outcomes, gain in life expectancy, longevity benefit, and prolongation of life [192-194]. Also, it should be noted that median ratios and HRs are measures that intrinsically involve a time aspect. A median ratio represents the timing of the event in the placebo vs. treatment group for the 50th percentile, and HRs average the instantaneous risk over a time period [195]. Methods for estimating time-based effect figures in some form include Cox proportional hazard modelling for survival-time (with time-varying covariates or not), Log rank tests, expected residual lifetime, expected (median and mean) survival time, accelerated failure time model, life table, and the Nelson-Aalen estimator [196-199].

A novel time-based measure, called Delay of Event (DoE), has been proposed for treatment evaluation [191]. The DoE approach uses time-to-event data, e.g., information about if a (binary) event has occurred or not, as well as the timing of that event, to estimate the effect as a time difference on the metric time scale. The measure uses the time points by which compared groups reach the same cumulative incidence proportion (percentile). Given that specific percentile, the DoE expresses the treatment benefit in terms of a delayed event. When calculating the measure, the proportions of events in each group are fixed and time is the estimated outcome [200]. The DoE can estimate effect regardless of follow-up time, in contrast to the median ratio, which requires that the study period extends until at least half of the study population has developed the event.

The DoE may be understood conceptually as the horizontal difference between a treatment arm and a control arm in a Kaplan-Meier curve at a given time point. Given a specific cumulative incidence and corresponding time point, DoE can be interpreted as the benefit in terms of how long the event is delayed due to the treatment, that is: the increase in event-free time. When outcomes such as mortality are investigated, the DoE depicts a prolonged survival time due to treatment. A negative DoE would imply that the event occurs earlier in the treatment group compared with in controls, in other words: a treatment harm or adverse event.

The DoE captures the effect size, or magnitude, and depicts it as the length of time by which an event would be delayed due to treatment, thus a period of time. Importantly, the DoE is conditional on the event, which means that it only applies to patients who would have developed the event during the follow-up period without the (superior) treatment.

DoEs may be calculated by using quantile or Laplace regression modelling, where Laplace regression is appropriate for censored percentiles and survival distributions [201-203]. DoEs can be estimated with corresponding 95% confidence intervals. The principle of using percentiles as outcomes in regression modelling has been proposed and discussed in other settings as well [200, 204-206].

A single DoE estimate relates to a specific percentile and corresponding treatment time, and it may be of interest to provide all DoEs over the full study follow-up. Such estimations can be graphically visualised through presenting DoE curves over time, such curves would show how an effect develops over follow-up: if it increases, decreases, or levels off. One example of such curve is seen in Figure 2, where DoE effects of ticagrelor over clopidogrel for the outcome death from vascular causes/MI or stroke are shown over follow-up, based on the Platelet Inhibition and Patient Outcomes (PLATO) trial [207].
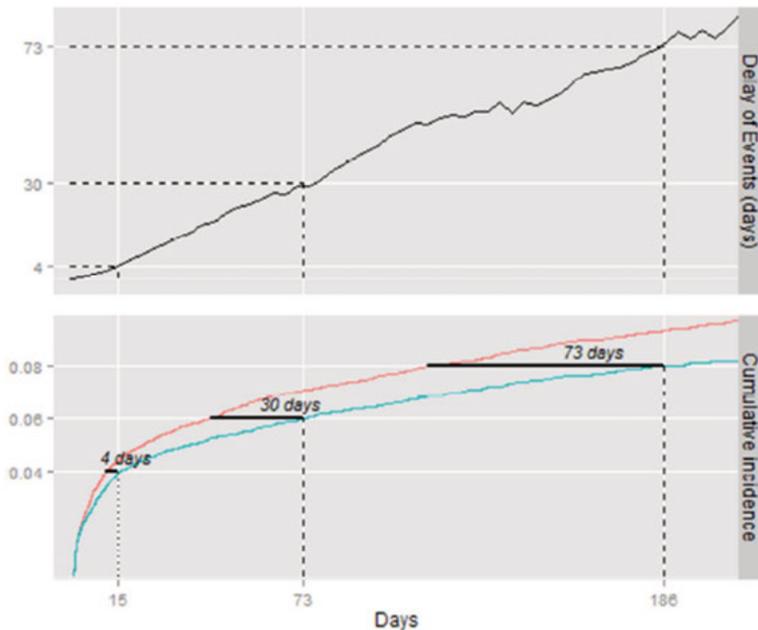
Figure 2. Delay of Events and cumulative incidence calculated for death from vascular causes/MI or stroke; this example comes from a comparison between ticagrelor and clopidogrel treatments in the PLATO trial [207].

In some medical fields, time-based formats are among the most established methods for estimating outcomes, an example is in oncology clinical trials, where the treatment benefit often compares median time to an outcome (e.g., death, tumour progression) in the treatment group to that in a control group. However, such comparisons rarely apply to studies of treatments in chronic diseases, such as CVD, where the incidence rates are low and follow-up does not extend until half of the patients have developed the event [189]. Time-based effect measures of treatment may be of interest in health communication and SDM, as such measures seem to be easier for lay people [208], patients [173], and health care professionals [174] to comprehend.

Rationale for the research project

Suboptimal adherence to treatments is prevalent across several common clinical conditions and populations [209]. A large number of hypotheses and factors explaining low adherence have been proposed through the years, but adherence is still a phenomenon that is far from fully explored [1, 210]. In particular, there are unexplored risk factors regarding the local environment and if these are associated with adherence and health-seeking behaviour. There is also little knowledge about adherence-enhancing strategies and how problematic adherence behaviour regarding preventive treatments can be modified.

When patients use preventive treatments they do not experience any direct effect of their medication use, and the absence of clear and self-assessed benefits for the individual may lower the motivation to continue taking the preventive medications as prescribed. It is instead, reasonable to assume that a patient's motivation to adhere to a preventive treatment is based on their belief in the benefit of the treatment, more or less abstractly captured in clinical trial results, recommendations, and encouragement from health care and pharmacy professionals, and others. However, treatment effect measures that are used in evaluations of clinical trials are usually relative measures, which may be difficult for lay people and patients to interpret. In addition, there is a lack of knowledge about how alternative effect measures compare to the established ones, in regard to effect estimations. Because of the lack of alternative effects estimations calculated from RCTs, there is also little knowledge on how people interpret, view, and respond to different prescription formats, and if there are potential benefits with the time-based DoE format in decision-making regarding preventive treatments.

Overall and specific aims

The overall aim of this thesis was to investigate factors associated with HSB and adherence, to use the DoE framework to estimate a preventive treatment effect regarding different anticoagulants, and to explore how the DoE measure compares to other effect measures in regards to people's views and intentions to initiate a preventive treatment. The specific aims for each study were as follows:

Study I

Study I aimed to investigate associations between self-reported general primary non-adherence and health-seeking behaviour, and environmental and social factors, in a sample from the general Swedish population.

Study II

Study II aimed to estimate effects of apixaban over warfarin as DoEs, that is the delays of stroke or systemic embolism, death, and bleeding outcomes due to apixaban use among AF patients in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial.

Study III

Study III aimed to investigate lay people's willingness to initiate and views of a hypothetical preventive treatment when the same effect size was described as DoE or as one of two established effect measures: relative and absolute risk reduction.

Study IV

Study IV aimed to investigate if the magnitude of an effect, when presented as different delay times in DoE, was associated with lay people's willingness to initiate and views of a preventive treatment.

Methods

Design

A quantitative population-based cross-sectional design was used for Study I. Study II used data from the randomised double-blinded clinical trial ARIS-TOTLE and estimated effects as DoEs. Studies III and IV were based on a randomised survey experiment comparing different ways of presenting the effects of a hypothetical preventive treatment and their associations to a person's willingness to initiate, and views on, the presented treatment. An overview of the studies conducted is presented in Table 1.

Table 1. Design, sample, data gathering and analysis used in the studies

Study	Design	Sample	Intervention	Outcome measures:	Analysis
I	Cross-sectional study	Men and women between 16 and 84 years of age (n = 100,433, response rate 52.9%)	-	Primary adherence and refraining from seeking health care	Pearson's chi-squared test, Mann-Whitney U test, and multiple binary logistic regressions models
II	Randomised double blind trial	18,201 patients with a mean age of 70 years, atrial fibrillation, and at least one additional risk factor for stroke	Treatment with apixaban or dose adjusted warfarin	Stroke or systemic embolism, death, major and intracranial bleeding	Laplace regressions for estimating DoEs[a] at six months, twelve months, eighteen months and twenty-two into the study period
III	Randomised survey experiment	Men and women between 40 and 75 years (n = 1,079, response rate 60.4%)	Information intervention of treatment effect as either: DoE,[a] RRR,[b] or ARR[c]	Willingness to initiate treatment, views on treatment, motivation to adhere, and WTP[d]	Chi-square analyses, Kruskal-Wallis H test, Mann-Whitney U test, and multiple logistic regression analyses
IV	Randomised survey experiment	Men and women between 40 and 75 years (n = 1,041, response rate 58.6%)	Information intervention of magnitude of the treatment delaying an event	Willingness to initiate treatment, views on treatment, motivation to adhere, and WTP[d]	Chi-square analyses, Kruskal-Wallis H tests, and multiple logistic regression analyses

[a]Delay of event. [b]Absolute risk reduction. [c]Relative risk reduction. [d]Willingness to pay.

Procedure, data collection and sample

Study I

Study I used data from the annual Swedish National Public Health Survey, "Health on Equal Terms," carried out from 2004 to 2014 [211]. The National Public Health Survey is a repeated cross-sectional postal questionnaire study that has been carried out on a yearly basis since 2004 by Statistics Sweden on behalf of the Public Health Agency of Sweden (previously the Swedish National Institute of Public Health). The questionnaire contains roughly 85 questions. Each year, 20,000 people from 16 to 84 years of age are randomly selected from the Swedish national population registry (from 2005 to 2007, 10,000 people were selected), adding up to a total of 190,000 persons for the time period. The questionnaires were returned by 100,433 individuals, making the response rate 52.9%.

Study II

Study II reassessed data from the ARISTOTLE trial, which was a multicentre study showing that apixaban was superior to warfarin in reducing the risk of stroke or other thromboembolic events in patients with AF or atrial flutter and at least one additional risk factor for stroke [30, 212]. The ARISTOTLE trial was carried out as a double-blind, double-dummy, randomised clinical trial including 18,201 patients from 1,034 centres in 39 countries, recruited between December 19, 2006, and April 2, 2010.

Studies III and IV

Study III and Study IV were based on a cross-sectional randomised survey experiment [213, 214], in a population-based sample. The sample consisted of 3,000 persons, aged between 45 and 75 years, who were randomly selected from the Swedish national population registry. The sample was then further randomised into five equally sized groups or "arms" (A, B, C, D, and E), which received different treatment effect information about a hypothetical cardiovascular treatment (see Table 2). The first group (A) received a treatment effect described as a RRR, the second group (B) received the same effect described as an ARR, and the third group (C) received information of the effect described as an 18-month Delay of Event. The arms A, B, and C displayed the same treatment benefit, but in different kinds of effect measures. The measures for these arms were derived from the Scandinavian Simvastatin Survival Study (4S), a randomised controlled trial presenting evidence that statin treatment improves health outcomes, such as major coronary events, in patients with established coronary heart disease [19]. Group

D received treatment effect information described as a 6-month DoE and group E received a description of a 1-month DoE. These numbers (in arms D and E) were not derived from any clinical trial, instead they were arbitrarily chosen to allow comparisons of magnitude variations in the DoE measure.

Table 2. Different ways of communicating treatment information

	Shared setting	Imagine that in the next five years you will have an increased risk of having a heart attack. Your physician offers you a drug with rare and mild side effects, to be taken in pill form once daily. The usefulness of the drug has been evaluated in scientific studies, and the effect can be described as follows:	
Group	**Effect measure**	**Figures/magnitude**	**Outlined text in survey**
A.	Relative risk reduction (RRR)	27%	If you take the treatment for five years, you will reduce the risk of a heart attack by 27%.
B.	Absolute risk reduction (ARR)	2%	Without treatment, your risk of a heart attack in the next five years is 8%, and if you take the treatment, the risk of a heart attack in the next five years will be 6%.
C.	Delay of Event (DoE)	18 months	If you have a heart attack in the next five years, it will be delayed by up to 1.5 years if you take the treatment.
D.	Delay of Event (DoE)	6 months	If you have a heart attack in the next five years, it will be delayed by up to 6 months if you take the treatment.
E.	Delay of Event (DoE)	1 month	If you have a heart attack in the next five years, it will be delayed by up to 1 month if you take the treatment.

For Study III, the first three arms where used (A, B, and C) where the treatment benefits were the same, but described in different formats. In Study IV, arms C, D, and E were used, where the formats were the same, but the magnitudes varied.

Data for Studies III and IV were collected from November 2013 to February 2014. The questionnaire was returned by 1,786 individuals, 51 persons were not possible to reach or declined to participate and 1,163 did not answer, making the response rate of the distributed questionnaires 60.6% (1,786/2,949). The response rate in the five groups varied from 56.8% to 65.2%. Those who declined to participate did so either by letter, email, or in a telephone call.

Subgroups, exploratory and background factors

Study I

Demographic data used in Study I were gender, age, and educational level (categorised as compulsory school, secondary school or equivalent, or university).

The local environment was investigated using two variables: housing type and behaviour based on perceived neighbourhood safety. Type of housing was categorised into three types: private house, condominium, and rented apartment, lodger, dorm or other. The private house category included bungalows and townhouses, and the condominium category included apartments in housing cooperatives (*bostadsrätt*) and actual condominiums. Housing cooperatives are the traditional form of owner-occupied apartment housing in Sweden; a member of the cooperative formally owns the right to use a specific apartment and inhabit it for an unlimited time, a right that can be bought and sold on the open real estate market. Membership in a housing cooperative is generally held to be the same thing as owning (as opposed to renting) an apartment. The last category included living in different types of rental housing.

Regarding the respondents' perception of their respective neighbourhoods, behaviour based on the perception of neighbourhood safety was used [215, 216]. It was assessed through the question: "Do you ever refrain from going out alone for fear of being attacked, robbed or otherwise molested?" Possible answers were "No," "Yes, sometimes," and "Yes, regularly." In the analyses, the question was dichotomised into "Yes" or "No" answers. Personal perceptions of environment are known to be better predictors of outcomes in some cases than several non-subjective, environmental measures [217].

The questionnaire contained the following question regarding perceived emotional social support: "Do you have someone you can share your innermost feelings with and feel confidence in?" The following question was used to assess perceived instrumental social support: "Can you get help from

someone/some people if you have practical problems or are ill?" Answers to these two questions were dichotomised into either "yes" or "no."

Data on informal caregiving was assessed with the following question: "Have you an ill or old relative or friend whom you help with daily activities, see to or nurse?" The answers were dichotomised into either "no" or "yes."

Financial problems was assessed using the question: "During the last 12 months, have you had difficulties managing your current expenses for food, rent, bills, etc.?" Answers to this question were dichotomised into either "no" or "yes."

Information about long-term illness was collected through the question: "Do you have any long-term illness, problems following an accident, any disability, or any other long-term health problem?" Replies were phrased as "no" or "yes."

Study II

Analyses of treatment effects as DoEs were performed in the total material as well as in subgroups. Subgroups were based on age, prior stroke, prior warfarin treatment, and the clinical centre's quality of warfarin treatment. The variables was dichotomised in the following ways. Age was dichotomised into older than 75 years of age, or 75 years of age or younger. Prior stroke was based on those without prior stroke or systemic embolism vs. those having such history. Similarly, prior warfarin treatment was dichotomised as those who had used warfarin before inclusion in the trial vs. not. Each trial centre's average time in therapeutic range (cTTR) was estimated using a linear mixed model for time in therapeutic range in the warfarin-treated patients, dichotomizing centres into below and above median cTTR. The median cTTR was used to distribute half of the study population to a centre with above median cTTR and the other half to a centre below median cTTR. This technique has been used earlier when controlling for the quality in warfarin use at the centre level in the ARISTOTLE trial [218].

Study III

Demographic data regarding the respondents' gender, age, and educational level (categorised as compulsory school, secondary school, or university) were used. Health-related factors regarding history of heart attack and/or angina were assessed, as well as whether the respondents were on current medical treatments, and if so, the number of prescribed drugs.

Study IV

Demographic data were collected using questions that assessed the respondent's gender, age, and educational level (categorised as compulsory school, secondary school, or university). Age was dichotomised into less than 60 years of age or 60 years of age or older for regression analysis. Data were collected using questions about history of CVD (dichotomised into having had myocardial infarction and/or angina, or not).

The Necessity-Concern Framework was used to address views of drug treatments [142], and, in Study IV, operationalised with the Beliefs about Medicines Questionnaire Specific version (BMQ-S) [142]. BMQ-S is a validated ten-item test instrument that assesses beliefs about perceived medication necessity and perceived medication concerns on five-point Likert scales. BMQ-S is a two-scale construct, where each scale has a possible range of scores from 0 to 20. The BMQ has been translated into Swedish, with a back translation approved by the original author of the questionnaire, and has been used in Sweden previously [58, 59, 219-221].

Clinical trial intervention in Study II

Patients with AF and at least one additional risk factor for stroke were randomly assigned (1:1) to receive either the NOAC apixaban (5 mg twice daily) or the VKA warfarin, with a treatment target of international normalised ratio (INR) 2.0–3.0. Randomization was stratified based on whether patients had received warfarin previously or not. The median length of follow-up was 1.8 years (interquartile range 1.5–2.4).

Information intervention in Studies III and IV

Study III

All respondents were asked to imagine that they were at increased risk of cardiovascular disease, and that their physician had suggested a preventive cardiovascular drug treatment. The text was phrased: "Imagine that in the next five years you will have an increased risk of having a heart attack. Your physician offers you a drug, with infrequent and mild side effects, which is to be taken orally once daily. The usefulness of the drug has been evaluated in scientific studies, and the effect can be described as follows:" This text was presented to all participants to get a shared setting. The identical setting was followed by information using an effect format specific to each group. The presented effect format was based on group allocation, where the first

group received information described as RRR (group A), the second group received information described as ARR (group B), and the third group received treatment effect described as DoE (group C). See Table 2. The different ways of describing the same treatment benefit, the "input data", were derived from the 4S, were the DoE figure in arm C was assessed at the end of the study period. The written information about the effects and the outcome questions were tested in a pilot study and modified afterwards before being included in this questionnaire.

Study IV

The setting in Study IV was the same as in Study III, but the effects presented were all in DoE format, but in different magnitudes. The groups received information about a treatment's effect as three different delayed event times of heart attack: 1 month (Group E), 6 months (Group D), or 18 months (Group C). See Table 2.

Outcomes

Study I

The outcomes in Study I were refraining from seeking medical care and primary adherence. Refraining from seeking health care was based on the question: "During the past three months, have you considered yourself in need of medical treatment but refrained from seeking it?" The response options were "no" or "yes".

Primary adherence was assessed with the question: "Have you, during the past three months, refrained from buying medicine you were prescribed?" The response options were "no" or "yes". Study I used data from the annual Swedish National Public Health Survey, from 2004 to 2014; the question used for the adherence outcome was not included in the questionnaire in 2007, and the refraining from seeking medical care question was not included in the questionnaires in 2005 and 2006.

Study II

The primary outcome in Study II was stroke (ischemic or haemorrhagic) and systemic embolism, the same as in the original ARISTOTLE trial [30]. Secondary outcomes were death from any cause and a composite measure of stroke, systemic embolism, death, or major bleeding. Safety outcomes consisted of major and intracranial bleeding. DoEs and corresponding percen-

tiles were estimated at six months, twelve months, eighteen months, and twenty-two months (median length of follow-up) into the study period.

Studies III and IV

Willingness to initiate preventive treatment and other questions that informed about people's views of the offered treatment were used as outcome variables in Studies III and IV. Willingness to initiate/accept treatment was assessed using the question: "If you were in the same situation as the person in this case, would you take the treatment?" Answers were dichotomous, "yes" or "no".

Other questions that were used to evaluate the views of the treatment were: "How much benefit do you assess that the drug would have?"; "Would you feel safe to take the drug?"; "Would you, based on the description, be motivated to take the medication on a daily basis?"; "How important is it to adhere to the treatment prescription?", and "To what extent does the description help you make a medical decision?". The answers to these questions were assessed on seven-point Likert scales ranging from 1 (not at all) to 7 (very much).

Willingness to pay (WTP) is an assessment of the (maximum) amount of money that would be paid by an individual to equalise a utility change [222]. To evaluate WTP, the contingent valuation method (CVM) was used. CVM is a questionnaire-based method first proposed as a method for eliciting market valuation of non-market goods and public goods [223, 224]. The method is widely used to elicit the monetary value a person is willing to pay for health care services [225], and likewise as a complementary measurement of the expected utility. In this study, the WTP was assessed through one open-ended question: "What is the maximum amount of money that you would pay per month during a five-year period to receive the treatment?". WTP was measured in Swedish currency (SEK), and for the purpose of this study was converted into Euros (€) at an exchange rate of 0.10.

Data analyses

Study I

Descriptive statistics were used for sociodemographic characteristics. Bivariate associations were investigated using Pearson's chi-squared test, the Mann-Whitney U test, and logistic regression models with corresponding confidence intervals (CI). Multiple binary logistic regressions were used to estimate associations between local environment, social support, caregiving status, financial status, long-term illness, and HSB or primary non-

adherence. A stepwise approach was used. Model 1 included housing type and refraining from going out due to perceived low neighbourhood safety. Model 2 included Model 1, social support and informal caregiving. Model 3 included Model 2 and demographics (gender, age, and education level), financial problems and long-term illness. All tests were two-sided and a p-value ≤ 0.05 was considered statistically significant. The Statistical Package for the Social Sciences (SPSS) version 22 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp Chicago, IL, U.S.A.) was used for the statistical analyses.

Study II

The effects of apixaban over warfarin were estimated as DoEs: the differences in time by which the same proportion of events have occurred in the two treatment groups [191, 226]. Given a specific percentile and corresponding time point in the less effective treatment (in this study warfarin), the DoE expresses the benefit in terms of how long the event is delayed due to the superior treatment (in this study apixaban), that is, the increase in event-free time.

DoEs were estimated by modelling survival percentiles with Laplace regression, a statistical method similar to quantile regression, but with the ability to handle censored data [201]. DoEs and corresponding 95% confidence intervals were estimated by fitting Laplace regression models. DoEs were estimated at six, twelve, eighteen and twenty-two months into the study period. The percentiles of the apixaban group at each time point were used as the bases for DoE calculations. The statistical analyses were performed with the statistical package R.

Study III

Proportional differences regarding willingness to initiate preventive treatment between randomised groups were tested using chi-squared analyses. The Kruskal-Wallis H test was used for outcomes of ordinal data. Sample size was determined prior to the study to have an 80% power to determine a 10% difference in proportion to the main outcome with a significance level of 0.05%. Pairwise comparisons were performed with the Mann-Whitney U test using Bonferroni correction to maintain the risk of a type 1 error at 0.05 [227]. In Bonferroni correction for pairwise comparisons among three groups, the significance level is set to a p-value ≤ 0.017 (0.05/3 ≈ 0.017). Binary logistic regression models were used to analyse associations between different effect descriptions and gender, age, education level, history of heart disease, number of prescribed medications, and willingness to initiate treatment. SPSS version 20 was used for all statistical tests.

Study IV

Chi-squared analyses and multivariate logistic regression analyses were used to investigate associations between willingness to initiate treatment and the independent variables. Multiple binary logistic regressions were used to estimate associations between length of time delay description in DoEs, and demographics, history of cardiovascular diseases, and NCF. A stepwise approach was used. Model 1 included length of time delay description, demographics, history of cardiovascular diseases, and NCF. Model 2 included Model 1 and multiplicative interaction terms of DoE descriptions × age group (categorised as over/under 60 years of age). The Kruskal-Wallis H test was used for outcomes regarding people's views and confidence in the treatment and for WTP. A p-value ≤ 0.05 was considered statistically significant. SPSS version 22 was used for descriptive statistics and statistical tests.

Ethical considerations

Study I used data from the annual Swedish National Public Health Survey, "Health on Equal Terms," which the Research Ethical Committee at the Swedish National Board of Health and Welfare has approved (December 8, 2003). Study I was further approved by the Regional Ethical Committee in Uppsala in November 11, 2013 (Dnr. 2013/390) and the extension of the project was approved in May 10, 2016 (Dnr. 2013/390/1).

Study II included analyses of data materials from the ARISTOTLE trial, the original study design of which has been approved by the appropriate national and institutional regulatory authorities and ethics committees. The approval of each institution review board was obtained before the inception of the trial, and patients gave written informed consent to participate [30, 212]. The ARISTOTLE trial is registered with ClinicalTrials.gov, number NCT00412984.

Studies III and IV were approved by the Regional Ethical Committee of Clinical Investigation in Uppsala in July 17, 2013 (Dnr 2013/269).

Results

Findings in Study I

In Study I, refraining from seeking medical care was reported by 15.1% (women 16.6% and men 13.4%), see Table 3. In the total material 6.1% reported primary non-adherence to prescribed medication. Among females, 6.4% reported non-adherence; the corresponding number among males was 5.7%.

Table 3. Distribution of characteristics among participants in Study I

		Male (N = 45,502)	Female (N = 54,931)	Total (N = 100,433)
Housing type	Private house	53.6**	49.6**	51.4
	Condominium	16.7**	18.2**	17.5
	Rented apartment, lodger, dorm or other	29.7**	32.3**	31.1
Refraining from going out due to perceived low neighbourhood safety	No	91.0**	65.5**	77.1
	Yes	9.0**	34.5**	22.9
Emotional social support	Yes	87.1**	90.8**	89.1
	No	12.9**	9.2**	10.9
Instrumental social support	Yes	94.3**	95.5**	95.0
	No	5.7**	4.5**	5.0
Informal caregiver	No	90.2**	88.2**	89.1
	Yes	9.8**	11.8**	10.9
Refraining from seeking medical care	No	86.6**	83.4**	84.9
	Yes	13.4**	16.6**	15.1
Primary adherence to medication	No	94.3**	93.6**	93.9
	Yes	5.7**	6.4**	6.1

Figures as percentages if not stated otherwise. Pearson's chi-squared test was used for distributions and Student's t-test was used for age testing for differences between men and women.
* $p \le 0.05$, ** $p \le 0.01$.

Logistic regression models showed that living in a rented apartment, lodger, dorm, or other was associated with refraining from seeking health care (adjusted OR 1.16, 95% CI 1.00–1.22). Refraining from going out due to perception of an unsafe neighbourhood was associated with refraining from seeking health care (adjusted OR 1.59, 95% CI 1.51–1.67). Lack of social support and being an informal caregiver were associated with refraining from seeking health care.

Logistic regression models showed that living in a rented apartment, lodger, dorm, or other was associated with primary non-adherence to medication (adjusted OR 1.22; 95% CI 1.13–1.31), see Table 4. Non-adherence was associated with refraining from going out due to perception of an unsafe neighbourhood (adjusted OR 1.26, 95% CI 1.17–1.36) and status as an informal caregiver (adjusted OR 1.19; 95% CI: 1.08–1.31). Lack of emotional and instrumental social support were associated with non-adherence.

Table 4. Results of logistic regression models of factors explaining primary non-adherence to medication in Study I

		Crude OR 95% CI	Model 1 OR 95% CI	Model 2 OR 95% CI	Model 3 OR 95% CI
Living environment	Housing type				
	Private house	1	1	1	1
	Condominium	1.26** (1.17 to 1.36)	1.19** (1.09 to 1.29)	1.13** (1.04 to 1.23)	1.13** (1.03 to 1.23)
	Rented apartment, lodger, dorm or other	1.71** (1.61 to 1.82)	1.61** (1.51 to 1.721)	1.46** (1.36 to 1.56)	1.22** (1.13 to 1.31)
	Refraining from going out due to perceived low neighbourhood safety				
	No	1	1	1	1
	Yes	1.52** (1.43 to 1.62)	1.46** (1.37 to 1.55)	1.39** (1.30 to 1.49)	1.26** (1.17 to 1.36)
Social support and informal caregiving	Emotional social support				
	Yes	1		1	1
	No	1.95** (1.81 to 2.09)		1.44** (1.32 to 1.57)	1.30** (1.18 to 1.42)
	Instrumental social support				
	Yes	1		1	1
	No	2.86** (2.62 to 3.12)		2.02** (1.80 to 2.26)	1.79** (1.59 to 2.01)
	Caregiver				
	No	1		1	1
	Yes	1.34** (1.23 to 1.45)		1.24** (1.13 to 1.35)	1.19** (1.08 to 1.31)

Odds ratio (OR), significance level, and confidence interval (CI) for primary non-adherence to medication.
* $p \leq 0.05$ ** $p \leq 0.01$. Model 1 = Housing type + refraining from going out due to lack of neighbourhood safety; Model 2 = Model 1 + Social support + informal caregiving; Model 3 = Model 2 + Demographics + financial problems + long-term illness (variables not shown in the table).

Findings in Study II

In the ARISTOTLE trial, 212 (2.32%) patients in the apixaban group developed stroke or systemic embolism; the corresponding numbers in the warfarin group were 265 (2.93%) [30]. The delay of stroke or systemic embolism due to apixaban as compared with warfarin use was 53 (95% CI -30 to 137) days at six months, 116 (95% CI 45 to 187) days at twelve months, 149 (95% CI 40 to 258) days at eighteen months, and 181 (95% CI 76 to 287) days at twenty-two months. See Table 1 in Paper II.

Death from any cause occurred in 603 (6.61%) patients in the apixaban group, and in 669 (7.37%) patients in the warfarin group, which corresponds to a delay of death from any cause of 52 (95% CI 17 to 87) days after six months, 58 (95% CI 8 to 107) days after twelve months, 57 (95% CI -6 to 121) days after eighteen months, and 55 (95% CI -4 to 114) days after twenty-two months of apixaban use. See Table 1 in Paper II.

Major bleeding occurred in 327 (3.60%) patients in the apixaban group and 462 (5.07%) patients in the warfarin group, and intracranial bleeding occurred in 52 (0.57%) patients in the apixaban group and in 122 (1.34%) patients in the warfarin group. The delay of major and intracranial bleeding due to treatment for twenty-two months was 206 (95% CI 130 to 281) and 392 (95% CI 249 to 535) days, respectively. See Table 1 in Paper II.

The composite outcome of stroke, systemic embolism, death, or major bleeding occurred in 1,009 (11.10%) patients in the apixaban group and in 1,168 (12.90%) patients in the warfarin group, with a DoE of 116 (95% CI 60 to 71) days after twenty-two months of apixaban use. See Table 1 in Paper II.

The continuous increase in gains in event-free time for stroke or systemic embolism, death from any cause, major and intracranial bleeding, and the composite outcome was illustrated by plotting DoEs against cumulative event rates in the compared arms and treatment time over the follow-up in. See Figures 1a-e in Paper II.

Results of analysis in the investigated subgroups for the primary outcome of stroke and embolism showed that the DoEs were numerically larger for subgroups of patients older than 75 years, patients with a history of prior stroke or prior warfarin treatment, and patients treated at clinic with poorer that median time in cTTR. See Table 2 and 3 in Paper II for results in subgroups.

Findings in Study III

In Study III, a total of 80.5% were willing to accept the treatment when the effect was described in terms of DoE, 83.0% when it was described as a RRR, and 62.8% when it was described as an ARR. Pairwise comparisons

revealed that there were statistically significant differences between DoE and ARR (p ≤ 0.001), and between RRR and ARR (p ≤ 0.001), but not between DoE and RRR (p = 0.396), see Table 5. In pairwise comparisons, DoE scored higher than ARR in assessments of benefit from treatment (p ≤ 0.001), motivation to take treatment (p ≤ 0.001), and importance to adhere (p = 0.005). RRR scored higher than ARR in assessments of benefit from treatment (p ≤ 0.001) and motivation to take treatment (p ≤ 0.001).

The median WTP for the three different treatment descriptions was €20 for DoE, €15 for RRR and €10 for ARR. In pairwise comparisons, WTP for treatment when the effect was described as DoE was statistically significantly higher than when the effect was described as ARR (p ≤ 0.001), WTP for the effect described as RRR was also statistically significantly higher than that of ARR (p = 0.008). There were no statistically significantly differences in WTP between DoE and RRR in pairwise comparisons (p = 0.353)

In logistic regressions, there was higher willingness to initiate treatment in the adjusted models when the effect was described as a DoE (OR 2.64, 95% CI 1.81–3.85) and RRR (OR 3.12, 95% CI 2.11–4.61) as compared with ARR (reference category).

Table 5. Treatment decision and views of treatment based on different treatment descriptions in Study III

Outcome	DoE	RRR	ARR	Overall	Test statistics	p-value
Willingness to initiate treatment, % (n)	80.5 (268)	83.0 (288)	62.8 (238)	75.0 (794)	47.24[a]	< 0.001
Use of information, md (q1, q3)	5 (4, 6)	5 (4, 6)	5 (4, 6)	5 (4, 6)	0.61[b]	0.736
Benefit from medication, md (q1, q3)	5 (4, 6)	5 (3, 6)	4 (2, 5)	4 (3, 6)	34.57[b]	< 0.001
Feel safe with medication, md (q1, q3)	4 (3, 6)	4 (3, 5)	4 (2, 6)	4 (3, 6)	2.29[b]	0.318
Be motivated to take medication, md (q1, q3)	5 (3, 6)	5 (4, 6)	4 (2, 6)	5 (3, 6)	27.56[b]	< 0.001
Importance to adhere, md, (q1, q3)	6 (5, 7)	6 (5, 7)	6 (4, 7)	6 (5, 7)	8.53[b]	0.014
Willingness to pay[c] (Euro), md (q1, q3), mean	20 (10, 30), 25.7	15 (10, 30), 22.9	10 (5, 25), 18.9	10 (8.3, 30), 22.5	13.17[b]	0.001

[a]Pearson chi-squared. [b]Kruskal-Wallis H test. [c]Willingness to pay was measured in Swedish krona (SEK) 1 SEK/0.10 Euro (€).

Findings in Study IV

In Study IV, the proportions accepting the treatment were 80.5% at DoE 18 months, 70.6% at DoE 6 months and 45.5% at DoE 1 month.

The odds of being willing to initiate treatment increased with longer DoEs, in adjusted models: odds ratio (OR) 5.51 (95% confidence interval (CI) 2.72–12.30) for a DoE of 6 months, OR 5.69 (95% CI 2.44–13.27) for a DoE of 18 months compared with a DoE of 1 month (reference category), see Table 6.

The median WTP for the three different treatment descriptions were €5 for DoE of 1 month, €10 for DoE of 6 months, and €20 for DoE of 18 months (p ≤ 0.001). The overall result in Study IV was that the longer the time periods presented in DoEs, the more favourably the respondents numerically answered the outcome questions regarding views of benefit from

treatment, feeling safe to take the drug, motivation to take treatment, importance of adhere and WTP.

Having a history of cardiovascular disease (heart attack and/or angina) was associated with having a higher willingness to initiate treatment in the crude and adjusted models (OR 2.86, 95% CI 1.11–7.36). A higher perceived necessity of medication in medical treatments in the NCF slightly increased the odds (OR 1.07, CI 1.03–1.11) for being willing to initiate therapy.

Table 6. Multivariate models of the odds of consenting to therapy due to magnitude in Study IV

		Crude OR 95% CI	Model 2 OR 95% CI	Model 3 OR 95% CI
Delay of Events (DoE)	Length of time delay			
	1 month (ref. cat.)	1	1	1
	6 months	2.88[**] (2.11 to 3.95)	4.45[**] (2.72 to 7.30)	5.51[**] (2.47 to 12.30)
	18 months	4.94[**] (3.50 to 6.97)	6.08[**] (3.61 to 10.23)	5.69[**] (2.44 to 13.27)
Demographic	Gender			
	Male (ref. cat.)	1	1	1
	Female	1.11 (0.85 to 1.43)	0.87 (0.56 to 1.33)	0.87 (0.57 to 1.32)
	Age group			
	under 60 years of age (ref. cat.)	1	1	1
	60 years of age or older	1.80[**] (1.35 to 1.28)	1.34 (0.87 to 2.07)	1.45 (0.76 to 2.70)
	Education level			
	University (ref. cat.)	1	1	1
	Secondary school or equal	1.43[*] (1.06 to 1.93)	1.13 (0.70 to 1.83)	1.12 (0.69 to 1.81)
	Compulsory school	2.28[**] (1.62 to 3.20)	1.87[*] (1.11 to 3.16)	1.89[*] (1.12 to 3.19)
History of cardiovascular diseases	History of heart attack or angina			
	No (ref. cat.)	1	1	1
	Had heart attack and/or angina	3.47[**] (1.62 to 7.41)	2.89[*] (1.13 to 7.41)	2.86[*] (1.11 to 7.36)
Necessity concerns framework[a]	Beliefs about medicine			
	Necessity	1.06[**] (1.03 to 1.10)	1.07[**] (1.03 to 1.11)	1.07[**] (1.03 to 1.11)
	Concern	1.03 (0.99 to 1.07)	1.00 (0.95 to 1.05)	1.00 (0.95 to 1.05)

Odds ratio (OR), significance level and confidence interval (CI) for willing to initiate therapy (0 = "no," 1 = "yes"). [a]Necessity and concern was used in index form, ranging from 0 to 20. *$p \leq 0.05$, ** $p \leq 0.01$. Model 1 = Length of time delay + demographics + history of cardiovascular diseases + Necessity concerns framework, Model 2 = Model 1 + Interaction effect (not shown in table).

Discussion

This section is a discussion of the results presented in this thesis regarding health-seeking behaviour, adherence to treatment, treatment effect estimations as Delay of Events from a RCT regarding anticoagulants, and how lay people perceived and responded to different effect formats.

Health-seeking and adherence in the general population

Most respondents in Study I did not report refraining from seeking medical care or being non-adherent to treatment. However, from a perspective of public health and equity in health care, the differences in adherence and health-seeking behaviour that were associated with environmental and social factors could be considered important.

In Study I, the results showed that not living in a private house and re-fraining from going out in the neighbourhood because of a perceived unsafe environment were separately associated with refraining from seeking medi-cal care and non-adherence to prescribed medication. Adherence behaviours to treatments regarding type 2 diabetes mellitus and human immunodeficien-cy viruses have previous been linked to environmental factors [228, 229]. The results in Study I are also in line with previous research that identified the perception of crime and violence as a predictor of health [230]. Fear of crime and safety-related worries are suggested to have an impact on behav-iour, potentially decrease physical activity [231], and limit personal freedom [216].

The results regarding housing and neighbourhoods in Study I may to some extent be explained by these factors being markers of socioeconomic status, which is known to have an impact on health behaviour [232]. Howev-er, other theories regarding this matter assert that the environment should not only be seen as a marker of socioeconomics [233]. Instead, the living envi-ronment may have a long-term effect on a resident's health in several ways, for instance through variations in land use, building quality, design, transpor-tation availability and infrastructure, access to nature/green/open spaces, public resources (e.g., services, health care, recreational opportunities), street condition, cleanliness/garbage maintenance, traffic volume, air quality, and noise [234-236]. Contextual factors may also be considered as mediators between socioeconomics and health, as socioeconomics may be linked to

health outcomes through environmental exposures associated with different accommodations [237, 238]. The results in Study I add that factors related to the environment may also affect different health behaviours such as adherence and health-seeking. These results have implications for the quality of health care, which involves the process and access of health services [239], including geographic/physical access to health care services [240, 241].

Social support is to some extent a contextual factor at the social micro environmental level [242]. In Study I, lower social support was associated with non-adherence to treatment, similar to previous studies regarding adherence [243, 244], lower social support was also associated with refraining from seeking medical care. In theoretical models, health behaviour is seen as an underlying link between social support and potential health outcomes [245, 246], and the hypothesis is that more social support is health-promoting because it facilitates healthier behaviours, such as getting help with transport to and from health care facilities. The results are also consistent with the Andersen's Behavioural Model of Health Services Use, which emphasizes both the community and the social context as important enabling factors for use of health care and access to care [130]. The results in study I points out that both factors found in the environment and social contextual layers were associated with health behaviors, which in the next step may impact health conditions among individuals according to the main determinants of health model by Dahlgren and Whitehead [131].

Informal caregiving could be considered a contextual social factor as well, as it concerns other people and related tasks in the individual's surrounding [247]. Informal caregivers often assist care receivers with help regarding medical concerns [248]. Hence, it is reasonable to assume that caregivers are familiar with both the health care system and the process of adherence to treatment, and that their knowledge would facilitate their own health behaviours. However, the findings in Study I indicate that being a caregiver was associated with poorer HSB and lower adherence in relation to the caregiver's own health care needs. These findings are also consistent with results in previous research [65, 249]. The mechanism behind the results might be the demanding and overall stressful situation that follows with the role as informal caregiver, which also results in well-known poor health outcomes [73, 250-253].

In 2009, a model was outlined that puts the relation of the caregiver and the care receiver in a shared micro environment, and other factors such as work and social contacts in the more external macro environment [247]. The model declares that the caregiver's situation is influenced by contextual factors, e.g., if the disease progresses and the care receiver takes up more space, the micro environment "swells out" into the party's living space, which could be at the expense of other occupations. The results in Study I indicate that health care is in the external environment when it comes to the caregivers' own medical needs. This puts the caregivers in an unusual situation, as

they themselves may have unmet health needs while also being part of the health care chain as informal care providers [254].

It may be advantageous for informal caregiver's to implement a new caring model which includes the present caregiver's own needs (not only knowledge and skills) as a part of patient care. Such a caregiver-receiver focused model could capture the caregiver's needs simultaneously with the care receiver's, and could be based on three major constructs: the care receiver's medical needs, health needs that are fulfilled by an informal caregiver, and the caregiver's own long-term needs that are required to function as a caregiver. If these three aspects could be equally considered, supported, and balanced, it may result in a sustainable and healthy caring situation for the patient-caregiver dyad. Established care models such as shared decision-making and patient-/person-centred care may also benefit by being complemented with such dimension.

Delay of events due to anticoagulants in AF patients

As discussed in the previous section, adherence to treatment may be influenced by many different factors, where some are hardly modifiable. However, a factor that is easier to modify within the health care is the health communication and what measures that are being used. Unfortunately, there has been a lack of alternative effect measures for use in health care, since most RCTs are not evaluated with other than relative effect measures. In study II an RCT of apixaban versus warfarin in AF patients was used for DoEs assessments.

The results in Study II showed that apixaban was superior to warfarin in terms of delaying stroke or systemic embolism, major and internal bleeding in patients with AF and an indication for oral anticoagulation. The DoE assessments confirmed previous results [30], and approximately six months of event-free time concerning stroke or systemic embolism was reached with apixaban, as compared with warfarin, after twenty-two mounts follow-up.

In addition, the DoE curves showed how the effect developed over the treatment period and the curves exposed different trends depending on outcome (see Figures 1a-e in Paper II). The DoE curve for stroke or systemic embolism and bleeding outcomes rose, almost linearly, immediately after treatment initiation and with no trend to level off during the study period. The outcome death from any cause provided a different picture, as the DoE developed fast after treatment initiation, reaching a statistically significant delay period within the first six and twelve months, and then did not continue to increase much.

Different results such as these might be explained by the properties of the DoE; DoE applies differently to different outcomes. Outcomes that might be entirely avoided, e.g., stroke, and bleeding, may show an infinite increase in

DoE with an effective treatment. Outcomes that will, or are very likely to, occur sooner or later, and thus are sensitive to competing risks such as the outcome death from any cause [9], may not show an infinite increase in DoE. With older age, competing risks will increase the risk of dying [10]. The median age of the study population was 70 years, an age where death is not unlikely to occur for several reasons, among them factors that anticoagulant treatments cannot prevent. Consequently, competing risks might be the reason why the effect of apixaban over warfarin on death from any cause seems to stop increasing during follow-up.

The presented DoE measures apply only to those who during a follow-up period would have developed the event of interest without using the superior treatment, i.e., would have experienced the event if they not had have apixaban. The individual interpretation of the results for a AF patient, who could have belonged to the study population, would be that stroke or a systematic embolism may be delayed by up to approximately six months when treated with apixaban as compared with warfarin, for twenty-two months of treatment use.

NOACs, such as apixaban, have a short half-life due to rapid decline of protective anticoagulation if treatment is discontinued [255, 256]. The NOACs' short half-life can be considered an advantage under some circumstances, such as for emergency surgery and in cases of bleeding due to accumulation of the drug in the blood [257]. A short half-life is also a disadvantage and a potential risk factor if adherence to treatment is low. For this reasons, guidelines often urges to educate AF patients about the importance of strict adherence to the prescribed dosing regimen and not forgetting to take the medication, preferably through shared decision-making and "shared accountability" [38, 255].

Effect measures, interpretation and decisions

As previously shown, a treatment effect can be estimated with different effect measures. However, there is little knowledge on how people interpret and react upon different effect measures. In Studies III and IV a hypothetical treatment description based on statins was carried out to a general sample. Statin treatment was applied in Studies III and IV since it is a common primary preventative drug used by large groups throughout the population [258].

In Study III, the same effect size was presented in three different formats (DoE, RRR and ARR), and in Study IV the same format was used in three different effect sizes (DoE of 18 months, 6 months and 1 month), to study willingness to initiate treatment and receiving of information.

In Study III, a higher proportion of individuals were willing to initiate the treatment when the effect was presented with DoE or RRR formats than with

ARR format. The results in Study III also implied that DoE and RRR were superior to ARR when it comes to giving patients positive views of benefits, motivation to adherence, as well as increasing WTP for the treatment.

Researchers have previously asked people directly about threshold values for life extension to make preventive drugs worthwhile. Average meaningful prolongation of life was reported to be somewhere around 12 to 18 months for cholesterol-lowering drugs [259], and meaningful 10-year statin benefit was 14 months for patients already using the drug [260]. In Study III, the gain in DoE was 18 months, making the results in Study III of relatively high acceptance to treatment somewhat consistent with the results in the previous studies, even if difference between the studies designs should be acknowledged. Previous research has also found evidence of the framing effect; that decision-makers are more likely to consent to therapy when presented with effects in RRR rather than in ARR format [175, 222].

In Study IV, the willingness to accept the proposed treatment increased with higher magnitudes in DoE. Also, respondents' views of the benefit from treatment, feeling safe to take the drug, motivation to take treatment, views on importance to adhere, and WTP were all associated with DoE magnitudes. The longer the time periods presented as DoEs, the more favourably the respondents expressed their views about the proposed drug. In Study IV, the setting was identical between the proposed treatments and a higher treatment benefit did not come with, e.g., an increased risk of side effects. The respondents' reactions to the magnitude increase seems rational based on the expected utility theory, in accordance with the expected utility theory a rational decision-maker will take the choice/action with the greatest expected total utility [170]. The results also indicates that lay people may understand the measure and that it provides information that applies to normative decision theory. These results are consistent with previous research which, in a similar way, tested decisions based on variations in postponement measures regarding hip fracture [208], and heart attack [193]. Previous research has also tested decision responses to different magnitudes in the RRR measure, which does not seem to help lay people to a sufficient extent in their decision-making [261].

In Study IV, a greater belief of treatment necessity was slightly associated with increased willingness to initiate therapy, and necessity beliefs about medications have in several studies been associated with adherence [58, 59, 146, 262]. Adjusting for necessity and concerns did not abolish the effect of an increased DoE magnitude on the outcome. The reason for including the NCF in Study IV was to adjust the analysis with responders' overall attitudes to drugs, rather than to measure specific necessity/concerns about the treatment presented in the hypothetical scenario. Different types of effect formats may affect preferences, which can be measured using frameworks like NCF. Usually preference measures are considered to be mediators between ac-

ceptance/adherence to treatment and the effect format, however in Study III the NCF was used for a different purpose.

Previous research has found that barriers to adherence may be due to a lack of understanding of the treatment effects and argues for increasing adherence by motivating patients through addressing beliefs about medications [263]. Studies indicate that improved communication quality between health care provider and patients may result in better adherence [56, 59, 85], and several adherence-enhancing methods and strategies include communication components [56, 85]. The link between communication and improved adherence might be a patient's preferences and beliefs, as also suggested by previous research that used beliefs as a mediating variable between treatment explanation and communication [59, 147]. This research also suggested that there were limited direct associations between treatment explanations/communication and adherence, which implies that adherence-enhancing interventions that use communication need to engender changes in preferences and beliefs to have an effect on adherence. Preferences and beliefs regarding treatments seem to be modifiable to some extent [172-175, 180]. When presenting treatment effects, the choice of format is a part of the clinical communication that shapes a patient's decision to accept or reject a proposed treatment [264].

Different people and groups interpret risk and health information differently; factors such as health knowledge and emotions may influence how risk is experienced [171]. Poor health literacy has been associated with low adherence [66-69], and poor health outcomes [265, 266]. Health literacy includes the ability to understand and use (written or verbal) health information in order to make appropriate health decisions and follow treatment instructions [267]. A central aspect in models of health literacy is the person's understanding and application of health information in the domains of health care, disease prevention, and health promotion [268]. Similarly, statistical illiteracy is the inability to understand and use the statistical results that permeate our daily lives [91]. Statistical illiteracy can cause misunderstandings and may make information exchange in various processes difficult [90]. Health and statistical literacy are individual factors, but are also dependent of communication, health information, and the context and process of health care [268].

Given the health and statistical literacy levels in the general population, some researchers advises health care and pharmacy professionals to use an uncomplicated and direct language (i.e., "living-room" language) [269], visual information in risk communication [270], and formulations based on absolute and frequentist terms are prompted for achieving insights in risk communication [88-90].

In a similar way, to increase the proportion of patient decisions that are informed in clinical practice, there might be a potential to improve communication by using familiar formats of effects that are easier to understand.

Among people with limited health or statistical literacy, this might be of particular importance when informing about treatment choices and potential outcomes of different decisions. The results from Studies III and IV imply that the time-based measure DoE is similar to RRR regarding acceptance of treatment at the same effect level (when compared with ARR), and that lay people seems to react rationally to the DoE magnitude variations. Thus, a higher proportion accepted the treatment when the effect magnitude was greater. The explanation for these results could be that people in general have more experience with assessing differences in time periods than probability ratios. Thus, time-based effect measures regarding treatments seem easier to understand and use as a basis for rational action. Time-based measures may be a component in a health communication strategy of value for patients with limited health or statistical literacy, where an uncomplicated and familiar language may be desirable.

DoE can also be visually displayed as DoE curves over treatment time. If the DoE effect magnitude develops as for the outcomes of stroke or bleeding in Study II (see Figure 1a, 1c and 1d in Paper II), with a steady increase throughout the treatment period, it may encourage patients to continue treatment and be adherent throughout a long-term therapy. It should be added that, it is not clear if people who are presented with effect curves are able to interpret them; observations have been made regarding framing effects [271], and sensitivity to the order of presentation [272].

In striving from a situation of uncertainty to one of greater certainty, different measures could be used in combination to increase clarity and risk minimization regarding outcomes that may be expected from a treatment [270]. Different measures can also provide knowledge regarding a certain aspects or dimensions of a treatment. In the case of time-based measures, such as DoE, the measures bring information regarding delays in periods. Statements about time periods can be understood in different ways. In consumer models, time is seen as a resource, and time is often considered to be more infungible and less transferable than other "types" of wealth, because it cannot be saved for future use [273, 274]. Uncertainties in relation to time may also be more aversive [273]. This makes planning in time especially important for individuals; also, uncertainties in time can disrupt planning, and make planning more difficult. Applied to a person's lifetime perspective, framing health in a period may be interpreted as a scarce resource than it frames a period when some actions or occupations can be possible or not. Measures that describes a time period, such as DoE, have the potential to help patients plan, which may facilitate medical decision-making.

However, it is not established that time-based figures necessarily lead to a higher acceptance/adherence; instead, people may find the time gain insufficient for a perhaps lifelong therapy, which may lead to lower acceptance and adherence [275, 276]. There are also large variations among health care pro-

fessionals and patients in what, to them, is a meaningful longevity benefit of a preventive CVD treatment [260, 277].

In concepts such as patient-centred care, informed, and shared decision-making, there is an expectation that if patients increase their understanding they will also improve their adherence [82, 159], and for drug effects that are perceived as high this is probably also true. But this might not be the case if a treatment effect is perceived as low, for if a patient perceives a treatment effect as low it may decrease his or her acceptance of, and adherence to, the treatment. From an adherence perspective, to avoid this; other descriptive tools not using effect measures or numeric presentations may be used in such cases (health communication does not always include effect measures or numeric presentations). Unfortunately, excluding comprehensible effect measures may be done at the expense of informed decision-making. This leads to an ethical dilemma: should the goal be to optimise adherence or to optimise understanding when facing treatment decisions in health care? In practice, however, this would not be a problem for most drug therapies. Rather, the challenge is to use comprehensible measures that help patients understand relatively substantial effects, which means that the objective of optimal adherence and increased informing coincide.

There is a critical difference between DoE and proportional measures such as RRRs and ARRs. Proportional measures depict treatment benefits as an increased chance of avoiding events, which is true within a limited study period. However, it is less likely to be true for all outcomes in a lifetime perspective. The effects of chronic diseases, which progress over the life course, are more likely to be delayed than fully avoided, from the preventive perspective [278]. Consequently, time-based measures like DoE, call for a shift in thinking regarding events of chronic disease as something that are possible to delay rather than fully avoid (depending on the outcome).

The DoE measure is conditional of the event, meaning that the effect applies only to those who will develop the event during a follow-up without treatment (or without the superior treatment). This means that patients have to assume that they will have the event in the time period corresponding to the clinical study follow-up to understand the benefit as DoE, and thereby need to implicitly face the question of their own absolute baseline risk. This is considered to be a limitation with the DoE measure in clinical practice, as it does not present a measure that directly applies to all patients at risk of an event, rather only those who would have the event (if treated with the control condition). On the other hand, preventive treatments may only have an effect on a certain event, in a given time period, in individuals who without the treatment would have developed the event, in that time period. Thus, the DoE format is an adequate measure of a preventive effect, depicting the magnitude of effect in those who actually benefit.

In clinical practice, a treatment's effects in terms of a DoE could be outlined to patients in the following way: "You have an increased risk of having

a [certain event], if you develop such event during the next [time period] it may be delayed by up to [delay period] due to [a certain] treatment." With the DoE results derived from the 4S (and used as treatment description in one arm in Studies III and IV) as an example, the statement could be outlined: "You have an increased risk of having a heart attack, if you develop such event during the next five years it may be delayed by up to approximately 1.5 years due to statin treatment."

The DoE information alone is not sufficient to provide complete information for treatment decisions; it needs to be complemented with other information. For example estimates of an individual's absolute baseline risk, as well as information about any side effects, how the treatment should to be taken, e.g., in pill form or other, how the treatment has been evaluated, and other measures regarding the effect, based on the individual case and situation. The potential value of using the effect estimates as DoE in clinical decision-making remains to be further investigated.

Methodological considerations

In Study I, a cross-sectional study was used to study health-seeking behaviour and treatment adherence in the Swedish population. The major advantage of this approach is its simplicity, providing a large sample sufficient for descriptive and analytical purposes. The main limitations of Study I include that data were self-reported and that the study design was cross-sectional. Using data from cross-sectional studies enables analyses of associations between variables, but the study type is generally considered insufficient to determine cause-effect relationships. Thus, in relation to the findings in Study I, it can be discussed if the directions of causality in the underlying assumption are appropriate or if there is a possibility of reverse causality and hypnotized directions could be the other way around. For example, that a poorer health-seeking behaviour and adherence might affect the amount of social support. Also, the study design cannot exclude confounders, i.e., that there is a third (not included) factor that influences both the independent variable and the outcome causing the observed association.

Most definitions and models of HSB concern a behaviour that arises from a perceived need. Also, in Study I the wording of the question about health-seeking behaviour was phrased as being based on a perceived need. However, in the case of chronic disease where prevention is a treatment alternative, the process of seeking access to such treatment usually works in a different way, as individuals rarely perceive themselves as having a current health problem defining their perceived need. Thus, this preventive setting poorly corresponds to definitions of HSB. However, the measure of HSB used in Study I was general.

In Study I, the outcome questions regarding health seeking and adherence have not been validated, which is a limitation in regard to their validity and reliability. Validity refers to how well an instrument measures what it is intended to measure, and reliability refers to how precise and consistent an instrument is. However, the outcome questions were phrased in a straight-forward way, thus seeming to have adequate face validity.

Variables used for living environment, demographics, social support, and informal caregiving were based on single items which minimises the risk of missing values, but it could also be argued that such items do not include all the dimensions of the constructs they set out to measure. In Study I, multi-variate analyses were perform to assess the sole association of living environment and social factors with the outcomes; there is a possibility that some unmeasured but important covariates were not included.

For the estimated DoE effect of apixaban over warfarin in Study II, the ARISTOTLE trial was used. The ARISTOTLE trial was a double-blind, double-dummy RCT. The ARISTOTLE trial study design holds low risk of biases and the study design is considered the highest standard for inferring a treatment's effect over a control. In Study II, the measuring points for the reported DoEs were arbitrary in the follow-up, and it can be discussed if these measuring points were the most appropriate.

For Studies III and IV, a five-armed randomised survey experiment was carried out using a population-based sample. The strengths of this approach include the randomised design and the information intervention. In Studies III and IV, a straightforward between-participant design was used to deter-mine associations between choices and evaluations regarding different as-pects of a hypothetical treatment. There are, however, other techniques for dealing with this type of question, such as threshold techniques, decision analysis, or probability trade-off techniques, discrete choice experiments, laboratory-based gambling, best–worst scaling, choice modelling, conjoint analysis, and more [274, 279, 280]. Most of these methods are performed as within-participant designs. The between-participant survey experiment de-sign used for Studies III and IV was chosen due to the objective; to seek responses (willingness, views and WTP) for specific pre-stated formats and magnitudes, rather than searching for attributes, levels, and combinations of attributes that most people would prefer, which is often the objective when using the within-participant design.

There are, however, several limitations with Studies III and IV. The study population was sampled from the general population, which is not the same as a patient population. The "input data" used to estimate the presented ef-fect in Study III came from a study investigating the effect in a secondary preventive setting, i.e., a population with existing coronary heart disease [19]. The majority of the respondents, however, most likely had a lower risk of CVD than the sample on which the presented figures were based. This circumstance might have made the statement less authentic for the respond-

ents and have implications for the results generalizability, i.e., external validity.

The use of a hypothetical setting is different from an authentic situation in several ways, such as in the perceived credibility of the sender and that higher perceived risks follow diagnosis, which might lead to psychological stress that could influence decision-making. The hypothetical setting might have affected the validity of the answers, and the respondent's choices and preferences in a non-hypothetical situation might differ from those in a hypothetical survey. A reasonable argument is that instead of carrying out this decision-making study in a general sample it would be more clinically relevant to use patients, for whom the effect measures actually apply. However, hypothetical scenarios are often used for simplicity and because they are suitable for initial testing of concepts, which may later be further tested in more specific populations. Another argument for starting with a general population and hypothetical setting is that it would be less ethically problematic than testing the usefulness of new concepts in a real-life situation. Studies III and IV were the first studies where people assessed the DoE format, which was a test of the format's feasibility. Overall, the benefits of carrying out an information intervention in a survey, instead of performing e.g. an observation study, exceed the shortcomings in this case, as the goal was to compare the receptions of different formats of effect measures.

Suggestions for future research

This thesis gives rise to several suggestions for future studies. There are multiple questions regarding health-seeking behaviour and adherence left to be addressed. Since both health-seeking behaviour and adherence depends on the specific situation, as well as the benefits and concerns of specific treatments, there is a need to study adherence in specific patient populations and contexts.

Regarding the use of time-based effect measures, the results in this thesis provide novel information about how a time-based effect may be assessed in the form of DoE. The DoE measure assessed the differences in timing when two groups have reached the same proportion of events, thus it expresses treatment effect as a time-based measure. This is a novel approach for assessing treatment effect. There is a need to test this new measure using empirical data from RCTs of other treatments, both to develop the methodology and to investigate DoEs of specific treatments for specific populations. It would also be possible to investigate if a combination of different formats of effect measures, both proportional comparisons and comparisons of timing of events, may provide more comprehensive information regarding treatment benefits. As a suggestion, such a measure could be based on studies of the areas under DoE curves. This could be estimated between two given outcome curves, summing up the effect in proportions as well as the time gain in a combined measure from a RCT.

Future research may also investigate the value of time-based measures in the context of clinical decision-making, for example investigating how patients and health care professionals understand the measure and if they believe it contributes to better understanding of treatment effects. It would be of value to investigate if the presentation of different effect measure formats affects short- and long-term adherence in longitudinal studies.

In Studies III and IV, the reception of DoE among lay people was investigated. Future studies should evaluate the reception and the DoE format's effect on decision-making in specific patient groups and for different treatments. There are several interesting subgroups to investigate regarding treatment format reception, such as people with different levels of medication aversion, limited health and statistical literacy, and people with a previous history of non-adherence. There is also a need to further investigate if time-based measures, such as DoE, may have an advantage in clinical decision-making and especially if they may impact adherence to treatment and/or

help patients with the interpretation of treatment effect. These types of questions should preferably be addressed through longitudinal designs.

In Studies III and IV, all participants shared the same (hypothetical) setting, this setup was chosen because of the objective: to investigate changes in responses generated only by the different effect formats. In addition, the DoE format should be investigated in various settings, to identify the conditions under which the measure is advantageous to use and how people react to different levels of disutility. This could be done in a within-participant design, such as a discrete choice experiment or similar, where several scenarios and attributes can be investigated in different combinations.

Conclusions

The results presented in this thesis lead to the following main conclusions:

- Living in rental housing and refraining from going out in the neighbourhood due to safety concerns were associated with refraining from seeking health care.
- Not living in a private house and refraining from going out in the neighbourhood due to safety concerns were associated with reporting non-adherence to prescribed medication.
- Less social support, being an informal caregiver, having financial problems, and long-term illness were associated with reporting non-adherence to treatment and refraining from seeking health care.
- Apixaban was superior to warfarin in terms of delaying stroke or systemic embolism, major and intracranial bleeding in patients with atrial fibrillation. The Delay of Event (DoE) assessments of treatment effects confirmed previous results and indicated that the magnitude of the effect was approximately six months' gain of event-free time concerning stroke or systemic embolism after twenty-two months of treatment use.
- Higher belief in treatment necessity was associated with higher willingness to initiate treatment in a hypothetical setting regarding statin therapy.
- Preventive treatment effects expressed in the DoE format were associated with a higher willingness to initiate treatment, positive views on treatment benefits, motivation to adhere, and willingness to pay for treatment, as compared with absolute risk reduction format, in lay persons facing a hypothetical treatment option.
- The willingness to initiate a preventive therapy was sensitive to the length of event-free time gain when the treatment effect was presented as the DoE among lay people in a hypothetical situation.
- Overall, the results imply that presenting treatment effect as DoE and relative risk reduction compare well in regard to accepting treatment at the same effect size level. Also, lay people seemed to react rationally to variations in DoE magnitudes when it came to their willingness to accept a proposed treatment, i.e., a higher proportion accepted the treatment when the magnitude of effect was greater in terms of gain in event-free time.

Clinical practice implications

Clinical practice implications of this thesis include:

- Considering a patient's living context, social support, long-term illness, and informal caregiving status when managing health-seeking behaviour and adherence to prescribed medication might be advantageous in health care policymaking and clinical practice.
- Estimations of treatment effects such as Delay of Events provide complementary information about how an effect develops over treatment time including estimations of the magnitude of that effect as an event-free time period.
- Displaying preventive treatment effects as estimations in terms of delays seem to be comprehensible to lay people, suggesting that it might be useful for presenting and communicating treatment effects in a clinical setting.
- The Delay of Event estimation might serve as a useful tool for communicating treatment effects to patients and increase the likelihood that patients will understand benefits, accept, and adhere to a preventive treatment.
- In clinical decision-making, when an informed decision-making process is desired, Delay of Event could be an effective measure to use, as people's willingness to initiate preventive therapy was sensitive to the length of time periods in the measure. Please see Table 7 for how to outline the Delay of Event measure when communicating treatment effects in clinical practice.

Table 7. How to present treatment effect results using the Delay of Event (DoE) approach in clinical practice

DoE statement outlined in general form:	*You have an increased risk of having a [certain event], if you develop such event during the next [time period] it may be delayed by up to [delay period] due to [a certain] treatment.*
DoE outlined with the results derived from the 4S and used (as one arm) in Studies III and IV:	*You have an increased risk of having a heart attack, if you develop such event during the next five years it may be delayed by up to approximately 1.5 years due to statin treatment.*

Svensk sammanfattning

Inledning

Ett problem i hälso- och sjukvården är att många behandlingar avbryts, eller aldrig ens påbörjas, och därmed inte kan få avsedda effekter för patienterna. Detta beskrivs som att en patient har låg följsamhet till sin behandling eller medicinering. Vad den låga följsamheten beror på är inte klarlagt, ett relevant antagande när det gäller förebyggande vård och behandling är att patienter avbryter sina behandlingar för att de inte känner någon omedelbar nytta av sin behandling. Det som istället kan vara avgörande för följsamheten är patientens egna tilltro till sin behandling. Patienternas egna preferenser och tilltro till behandlingen kan alltså vara det mest centrala för om en patient fortsätter med sin behandling eller inte. I praktiken handlar det alltså om att; när en patient tror att ett läkemedel kan minska risken för en åkomma, kommer denna också att använda sitt förskrivna läkemedel – annars inte. Den tilltro och uppfattning som patienter har om olika behandlingar är i viss mån modifierbar och kan eventuellt påverkas av kommunikationen inom hälso- och sjukvården.

Trots att det är viktigt att patienter förstår effekterna av olika behandlingar är de mått och beskrivningar av läkemedelseffekter som idag vanligen används svåra att förstå för många patienter. De mått som vanligen förekommer och anses metodiskt tillförlitliga är ofta baserade på proportioner, kvoter och procent. Vanliga mått i dessa sammanhang är relativ riskreduktion (RRR) och absolut riskreduktion (ARR). Dessa mått är beräknade och uttrycks med hjälp av gruppjämförelser ofta i procenttal, vilket gör det än svårare att förstå när ett riskminskningsmått ska användas för en enskild patient.

Utöver de procentbaserade effektmåtten har det utvecklats nya effektmått som istället uttrycker behandlingseffekten i form av en tidsperiod, alltså som den förskjutning av en viss sjukdomshändelse som uppstår tack vare en behandling. Ett av dessa tidsperiodsbaserade effektmåtten är "Fördröjning av händelse" (på engelska: Delay of Event, DoE). Måttet är baserat på den tidsskillnad som kan beräknas när den kumulativa incidensen i två (behandlings-) grupper når samma nivå (percentil). Måttet uttrycker behandlingsnyttan som en tidsfördröjning av en sjukdomshändelse, t.ex. en hjärtinfarkt. DoE-måttet är betingat av händelsen, vilket innebär att det bara gäller för patienter som skulle ha utvecklat händelsen utan (den bättre) behandling under den

uppföljningsperiod som estimatet gäller. DoE visar tiden som en händelse skulle fördröjas på grund av behandlingen, och estimerar därmed effektstorleken uttryckt som en förlängning av en sjukdomsfri tidsperiod (för den specifika sjukdomen/sjukdomarna som uppmäts).

Syftet med den här avhandlingen har varit att genom fyra studier analysera vårdsökningsbeteenden och följsamhetsproblematiken i Sverige, utprova det nytt tidsbaserat effektmåttet DoE vid förebyggande behandling, samt undersöka hur människor i allmänhet förstår tidsbaserade mått för behandlingseffekt. De specifika syftena för studie I-IV var följande:

Studie I syftade till att studera kontextuella och sociala faktorers betydelse för följsamhet till läkemedelsbehandlingar och vårdsökningsbeteende.

Studie II syftade till att estimera effekten av apixaban kontra warfarin med det nya tidsperiodsbaserad måttet DoE i en klinisk prövning avseende antikoagulantiabehandling vid förmaksflimmer, och utfallen stroke eller emboli och blödning.

Studierna III och IV syftade till att jämföra hur människor i allmänhet reagerade på olika effektmått. I studie III ställdes det tidsbaserade måttet DoE mot de två etablerade effektmåtten RRR och ARR, med avseende på behandlingsacceptans. I studie IV jämfördes tre olika effektstorlekar, alltså olika långa tidsperioder i DoE-måttet, i syfte att undersöka om människor i allmänhet reagerade rationellt utifrån effekten av det läkemedel som beskrevs.

Metod

Studie I var en enkätstudie till slumpvist utvalde personer i hela Sverige, där enkäten besvarades av sammanlagt 100 433 personer (svarsfrekvens 52.9%). Datainsamlingen genomfördes av (dåvarande) Folkhälsoinstitutet (nuvarande Folkhälsomyndigheten) genom en årlig enkät och i studie I används data från åren 2004 till och med 2014. Deltagarna besvarade frågor om följsamhet, vårdsökningsbeteende, levnadsmiljö och social situation. Analyserna genomfördes med justerade regressionsmodeller.

Studie II använde data från den randomiserad kliniska prövningen Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) för att beräkna DoEs som en skillnad i tid till olika utfall mellan apixaban- och warfaringrupperna, när en lika stor andel i respektive behandlingsgrupp hade drabbats av den aktuella händelserna. Utifrån den specifika percentilen uttrycker sedan DoE behandlingseffekten som en fördröjning av den aktuella händelsen. De utfall som användes var stroke eller systemisk emboli, mortalitet oavsett orsak och blödningar. DoEs estimerades vid fyra tidpunkter: sex, tolv, arton och tjugotvå månader in i uppföljningen. I analyserna tillämpades Laplaceregression, vilket är en typ av kvantilregression som fungerar bra på censurerad data.

Studierna III och IV byggde på ett randomiserat enkätexperiment där olika personer randomiserades till en viss beskrivning av en hypotetisk behandling. I studie III användes samma storlek på behandlingseffekt i tre olika effektformat; DoE jämfördes med ARR och RRR, baserade på den skandinaviska statinstudien 4S. I studie IV presenterades olika effektstyrkor, som olika långa tidsperioder, i samma format (DoE). Utfallen i båda studierna var att svara "ja" respektive "nej" på frågan om man skulle acceptera föreslagen behandling, samt deltagarnas tilltro och betalningsvilja till den behandling som föreslogs. För studierna III och IV används deskriptiv statistisk och logistiska regressionsanalyser.

Resultat

Resultaten av studie I visade att såväl sociala som kontextuella faktorer i närmiljön hade samband med följsamheten till läkemedelsbehandling och vårdsökningsbeteendet. Sociala faktorer med associationer till hälsobeteendena var socialt stöd och informell vårdgivning. Vad gäller de kontextuella faktorerna, alltså faktorer i närmiljön, hade typ av boende och om man uppfattade säkerhetsproblem i sitt område samband med att inte söka vård och inte följa föreskriven behandling. Även att rapportera långvariga sjukdomar var associerat med hälsobeteendena.

Resultaten av studie II visade att patientgruppen som fick behandlingen apixaban hade en fördröjning av stroke eller systemisk emboli på 181 (95% konfidensintervall (KI) 76 till 287) dagar jämfört med warfaringruppen, tjugotvå månader in i studien. Mortalitet oavsett orsak i apixabangruppen fördröjdes med 55 (95% KI -4 till 114) dagar jämfört med warfaringruppen, tjugotvå månader in i studien. Fördröjningen av större blödning i apixabangruppen var 206 (95% KI 130 till 281) dagar jämfört med warfaringruppen, tjugotvå månader in i studien.

Resultaten av studie III visade att 81% var villiga att (hypotetiskt) påbörja en behandling beskriven med DoE-formatet, 83% med formatet RRR och 63% med formatet ARR.

Resultaten från studie IV visade att 81% var villiga att (hypotetiskt) påbörja en behandling med DoE som gav 18 månaders fördröjning av hjärtinfarkt, vilket kan jämföras med 71% och 46% när effekten beskrevs som en DoE på 6 respektive 1 månad. Resultaten i studie IV visade även att deltagarnas tilltro och betalningsvilja till den behandling som föreslogs varierade med den presenterade effektstorleken.

Diskussion

Avhandlingens resultat kan tolkas som att följsamheten till läkemedelsbehandling och vårdsökningsbeteendet påverkas av flera olika faktorer. Vissa av dessa faktorer finns troligen i personernas närmiljö och i sociala relationer, och vissa faktorer har mer att göra med personernas egna föreställningar, värderingar och tilltro.

Resultaten av studie II bekräftade tidigare resultat som visar att apixaban är en effektivare behandling än warfarin för patienter med förmaksflimmer. Resultaten visade att apixaban fördröjer stroke eller systemisk emboli med en sjukdomsfri period på ungefär sex månader i jämförelse med warfarin, efter tjugotvå månaders behandling.

Studie III visade att ungefär lika många personer var villiga att (hypotetiskt) påbörja en behandling beskriven med DoE- och RRR-formaten, men färre var villiga att påbörja behandlingen när effekten beskrevs i termer av ARR. Studie IV visade att färre personer var beredda att acceptera en behandling när effekten i DoE-beskrivningen beskrevs som svagare, än när den beskrevs som starkare. Resultaten kan tolkas som att människor förstår styrkevariationer i måttet DoE och förefaller kunna fatta rationella (hypotetiska) beslut utifrån måttet.

Därmed är det rimligt att anta att DoE kan ha en förtjänstfull roll inom sjukvården där ett uttalat mål ofta är att patienter ska vara införstådda med olika behandlingsalternativ. Om DoE ska användas inom sjukvården är det viktigt att måttet beskrivs korrekt och med hänsyn till att måttet är betingat av den händelse som fördröjningen beskriver under en viss tidsperiod.

Följande formulering bör användas vid presentation av preventiv behandlingseffekt utifrån DoE-måttet: "Du har en ökad risk att drabbas av [viss händelse], om du utvecklar en sådan händelse under den närmaste [tidsperioden] kan den fördröjas med upp till [förskjutningsperiod] om du använder [en viss] behandling." Om man utgår från de effektsiffror som baserades på 4S och användes i en arm i studie III respektive studie IV, blir DoE-formuleringen följande: "Du har en ökad risk att drabbas av hjärtinfarkt, om du utvecklar en sådan händelse under den närmaste fem åren kan denna fördröjas med upp till 1,5 år om du använder statinbehandling."

DoE måttet i sig är dock inte tillräcklig för att ge fullständig information inför ett behandlingsbeslut, utan bör kompletteras med annan information, till exempel med proportionsbaserade effektmått, samt information om biverkningar, hur behandlingen ska tas, utifrån det enskilda fallet och situationen. Det potentiella värdet av att använda DoE i kliniskt beslutsfattande återstår att undersökas ytterligare.

Slutsatser

Följande slutsatser kan dras utifrån resultaten som presenteras i denna avhandling:

- Faktorer i närmiljön, som boende och att avstå från att gå ut i grannskapet på grund av otrygghet, hade samband med vårdsökningsbeteende och följsamhet till föreskriven behandling.
- Mindre socialt stöd, att vara en informell vårdgivare och att ha ekonomiska problem hade samband med bristande följsamhet till behandling och att avstå från att söka vård.
- Apixaban var effektivare än warfarin med att fördröja sjukdomsevent som stroke och blödningar, hos patienter med förmaksflimmer.
- Högre tilltro till läkemedelsbehandlingar var förknippat med ökad vilja att (hypotetiskt) inleda statinbehandling.
- Effektformaten DoE och RRR var jämförelsevis lika i avseende att nå acceptans för en (hypotetisk) behandling. Människor i allmänhet verkade också reagera rationellt på variationer i DoE, dvs. en högre andel accepterade behandlingen när effekten beskrevs men en längre sjukdomsfri tidsperiod, än med en kortare tidsperiod.

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No man is an island – John Donne (1624)

Den här avhandlingen har bland annat studerat läkemedelsanvändning och relaterade beteenden i sin kontext – alltså där, i vid bemärkelse, företeelsen sker. Precis som avhandlingsämnet sker alla mänskliga aktiviteter i ett sammanhang, detta gäller i allra högsta grad också den här avhandlingens tillblivelse. Listan på personer som varit delaktiga och på olika sätt haft betydelse för mig kan göras mycket lång och utöver de personer som nämns finns en rad personer som direkt eller indirekt bidragit till forskargärningen. I enlighet med epidemiologins modell om "uppströms" och "nedströms" faktorer börjar jag med de som varit närmst frambringande för denna avhandlings tillblivelse och framläggande.

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