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Use of secondary preventive drugs after stroke

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Säll är den som har till rättesnöre, att man bör tänka efter före.

Tage Danielsson (1928-1985)

Original papers

This thesis is based on the following papers:

I. Glader EL, Sjölander M, Eriksson M, Lundberg M. Persistent use of secondary preventive drugs declines rapidly during the first 2 years after stroke. Stroke. 2010 Feb;41(2):397-401.

II. Sjölander M, Eriksson M, Glader EL. Few sex differences in the use of drugs for secondary prevention after stroke: a nationwide observational study. Pharmacoepidemiol Drug Saf. 2012 Sep;21(9):911-9.

III. Sjölander M, Eriksson M, Glader EL. Social stratification in the dissemination of statins after stroke in Sweden. Eur J Clin Pharmacol. 2013 May;69(5):1173-80.

IV. Sjölander M, Eriksson M, Glader EL. The association between patients' beliefs about medicines and adherence to drug treatment after stroke: a cross-sectional questionnaire survey. BMJ Open 2013;3:e003551. doi:10.1136/bmjopen-2013-003551.

The original papers will in the cover story be referred to by the Roman numerals.

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Abbreviations and explanations

ACE	Angiotensin Converting Enzyme
ADL	Activities of Daily Living
ARB	Angiotensin Receptor Blocker
ASA	Acetylsalicylic Acid
AVAIL	Adherence eValuation After Ischemic stroke Longitudinal Registry
BMQ	Beliefs about Medicines Questionnaire
Brief IPQ	Brief Illness Perception Questionnaire
CHA_2DS_2-VASc	Risk score for stroke in patients with atrial fibrillation
ICD-10	International Classification of Diseases, the 10th revision
IPQ-R	Illness Perception Questionnaire-Revised
LISA	Longitudinal integration database for health insurance and labour market studies
MARS	Medication Adherence Report Scale
NPR	National Patient Register
RCT	Randomised Controlled Trial
SRM	Self-regulatory model
TIA	Transient Ischemic Attack
WHO	World Health Organisation

Abstract

Background Stroke is a serious condition that can have significant impact on an individual's health and is a significant burden on public health and public finances. Secondary preventive drug treatment after stroke is important for decreasing the risk of recurrent strokes. Non-adherence to drug treatment hampers the treatment effect, especially in long-term preventive treatments. The aim of this thesis was to study the use of secondary preventive drugs after stroke among Swedish stroke patients in terms of inequalities in implementation in clinical practice and patient adherence to treatment over time.

Methods Riks-Stroke, the Swedish stroke register, was used to sample stroke patients and as a source of information on background characteristics and medical and health care-related information including information on prescribed preventive drugs. The patients that were included had a stroke between 2004 and 2012. Individual patient data on prescriptions filled in Swedish pharmacies were retrieved from the Swedish Prescribed Drug Register and used to estimate patient adherence to drug treatment. Data on education, income, and country of birth were included from the LISA database at Statistics Sweden. A questionnaire survey was used to collect information about patients' perceptions about stroke, beliefs about medicines, and self-reported adherence.

Results Results showed that a larger proportion of men than women were prescribed statins and warfarin after stroke. There was also a social stratification in the prescribing of statins. Patients with higher income and a higher level of education were more likely to be prescribed a statin compared to patients with low income and low level of education. Statins were also more often prescribed to patients born in Nordic countries, Europe, or outside of Europe compared to patients born in Sweden. Primary non-adherence (not continuing treatment at all within 4 months of discharge from hospital) was low for preventive drug treatment after stroke. Data on filled prescriptions, however, indicated that the proportion of patients who continued to use the drugs declined during the first 2 years after stroke. For most drugs, refill adherence in drug treatment was associated with female sex, good self-rated health, and living in institutions and (for antihypertensive drugs and statins) having used the drug before the stroke. For statins and warfarin, a first-ever stroke was also associated with continuous drug use. Self-reported adherence 3 months after stroke also showed associations with patients' personal beliefs about medicines; non-adherent patients scored higher on negative beliefs and lower on positive beliefs about medicines.

Conclusion Inequalities between men and women and between different socioeconomic groups were found in the prescribing of secondary preventive drugs

after stroke. Only a small proportion of Swedish stroke patients did not continue treatment after discharge from hospital, but the proportion of non-adherent patients increased over time. Poor adherence to preventive drug treatment after stroke is a public health problem, and improving adherence to drug treatment requires consideration of patients' personal beliefs and perceptions about drugs.

Key words: stroke, secondary prevention, drug use, equality, medication adherence, medication beliefs

Sammanfattning på svenska

Användning av sekundärpreventiva läkemedel efter stroke

Bakgrund: I Sverige drabbas varje år ca 30 000 personer av stroke. Stroke är en av de främsta orsakerna till sjuklighet, handikapp och död i västvärlden. På grund av de konsekvenser som stroke innebär, både för enskilda individer och för samhället, är det viktigt att försöka förhindra återinsjuknanden. Sekundärpreventiva läkemedel som förskrivs efter stroke påverkar riskfaktorer för stroke och minskar risken för nya insjuknanden. I nationella riktlinjerna för strokevård finns rekommendationer om hur dessa läkemedel bäst används.

Enligt den svenska Hälso- och sjukvårdslagen har alla människor rätt till vård på lika villkor. För en jämlik vård krävs att alla människor har samma tillgång till bland andra sekundärpreventiva läkemedel efter stroke. Eftersom alla dessa läkemedel är receptbelagda bör förskrivningen inte skilja mellan olika grupper i samhället.

Världshälsoorganisationen, WHO har uppskattat att patienters följsamhet till långtidsbehandling vid kroniska sjukdomar är i genomsnitt 50 %. Det är därför viktigt att undersöka i vilken utsträckning patienterna faktiskt forsätter preventiv behandling efter stroke samt att undersöka vilka faktorer som är relaterade till fortsatt behandling. Även sambanden mellan följsamhet och patienters egna uppfattningar om stroke och läkemedel är viktiga att kartlägga.

Syftet med denna avhandling var att studera användningen av förebyggande läkemedel bland svenska strokepatienter, både vad gäller ojämlikheter i användning av läkemedel i klinisk praxis och patienternas följsamhet till behandlingen över tid samt vilka faktorer som visade samband med följsamhet.

Metod: De patienter som studerats drabbades av stroke mellan 2004 och 2012 och är registrerade i det nationella kvalitetsregistret för strokevård, Riks-Stroke. Under de aktuella åren registrerades 80 – 90 % av alla strokepatienter i Sverige i Riks-Stroke. I registret finns information om patienterna både före insjuknandet, under sjukhusvistelsen och från uppföljningar gjorda efter utskrivningen. I registret finns också information om vilka förebyggande läkemedel som förskrevs vid utskrivningen från sjukhus.

Genom personnumret kunde data från Riks-Stroke kopplas ihop med data från ett register där alla köp av receptbelagda läkemedel på svenska apotek registreras (Läkemedelsregistret). Det var möjligt att följa om strokepatienterna fortsatt köpa ut sina ordinerade läkemedel. Patienternas köp av läkemedel följdes i upp till 2 år

efter utskrivning från sjukhus, och patienterna klassades som följsamma så länge de köpte ut läkemedel minst en gång i varje fyramånadersperiod.

För att undersöka skillnader mellan grupper med olika inkomst, utbildning och födelseland kompletterades data även med information från SCB (Statistiska centralbyrån).

De faktorer som undersökts för samband med patientföljsamhet är patientrelaterade (ex. ålder, kön, personliga uppfattningar om läkemedel och stroke), sjukdomsrelaterade (ex. tidigare stroke, andra sjukdomar), vårdrelaterade (ex. typ av vård, nöjd/missnöjd med vården) och läkemedelsrelaterade (läkemedelsanvändning innan stroke). För information om strokepatienters uppfattningar om stroke och läkemedel skickades en enkät ut till ett urval patienter. Enkäten innehöll frågor om stroke, frågor om personliga uppfattningar om nytta och risker med läkemedel, men också frågor om beteende för att skatta patienternas följsamhet till behandling.

Resultat: Blodfettssänkande läkemedel och det blodförtunnande läkemedlet *warfarin* skrevs i högre utsträckning ut till män än till kvinnor efter stroke. Det fanns också skillnader i förskrivning av blodfettssänkande läkemedel mellan olika sociala grupper. Patienter med lägre utbildning och lägre inkomst ordinerades i lägre utsträckning blodfettssänkande läkemedel efter stroke jämfört med patienter med hög utbildning och inkomst. Vid undersökning av skillnader i förskrivning av blodfettssänkande läkemedel mellan grupper födda i olika länder framkom att en mindre andel av personer födda i Sverige fick blodfettsänkande läkemedel jämfört med personer födda i andra länder.

De allra flesta patienter som förskrevs förebyggande läkemedel efter stroke fortsatte behandlingen efter att de lämnat sjukhuset. Bara mellan 4 och 11 % beroende på läkemedel, fortsatte inte behandlingen direkt efter utskrivningen. Genom att under 2 år följa vilka läkemedel patienterna fortsatte hämta ut på apotek kunde vi dock konstatera att användningen av dessa läkemedel minskade över tid. Mellan 25 och 50 % av patienterna hade efter 2 år avbrott i uthämtning av läkemedlen på apotek.

Fortsatt användning av läkemedel var för de flesta läkemedel eller grupper av läkemedel associerade med att patienten skattat sin hälsa som god, med kvinnligt kön, med att bo på någon typ av institution, och för blodtrycks- och blodfettssänkande läkemedel, med att ha använt läkemedlet innan man insjuknade i stroke. För blodfettsänkande läkemedel och warfarin var också fortsatt användning vanligare bland patienter som haft sin första stroke jämfört med patienter som haft stroke tidigare. Patienternas följsamhet till behandlingen var också associerad till personliga uppfattningar om läkemedel. De patienter som

själva uppgav att de inte alltid var följsamma till behandlingen var mer oroliga för negativa effekter av läkemedel samt hade lägre tilltro till läkemedels positiva effekter och till att de själva skulle ha nytta av behandlingen.

Slutsats: Denna avhandling visar på ojämlikheter i förskrivning av sekundärpreventiva läkemedel mellan män och kvinnor och mellan olika sociala grupper. Patienternas användning av rekommenderade läkemedel var den närmast tiden efter strokeinsjuknandet hög, men minskade under de första två åren efter en stroke. Dålig följsamhet till förebyggande behandling efter stroke är därför ett folkhälsoproblem. Det är viktigt att undersöka vilka uppfattningar och attityder patienterna själva har till läkemedel och ta hänsyn till detta vid insatser som görs för att förbättra användningen av läkemedlen.

Background

Stroke and stroke prevention

Stroke is a serious condition that affects approximately 30 000 people a year in Sweden.[1] The World Health Organisation (WHO) definition of stroke is "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 h or longer, or leading to death, with no apparent cause other than of vascular origin".[2] A stroke can be caused by a cerebral infarction or an intracerebral or subarachnoid hemorrhage. In Sweden, approximately 85% of all strokes are caused by infarctions.[3]

The age-specific incidence of stroke in Sweden has decreased in the older and middle-age groups where most strokes occur, but it has increased in ages younger than 45 years.[1, 4] Mortality has also decreased.[4] The average age for suffering a stroke in Sweden is 73 years for men and 78 years for women[3], and this age difference between men and women is consistent with international findings.[5] The age-adjusted incidence of stroke has been shown to be higher in men[5, 6], but the total number of both strokes and stroke deaths are higher in women.[6] Studies have also shown an increased risk of stroke with decreasing socioeconomic status.[7-9] A study from northern Sweden showed a higher incidence of first-ever stroke in low educated groups even after controlling for age and sex.[10]

In a study from the south of Sweden, 6.8% of stroke patients died within 28 days and 11.8% within 1 year of the event.[7] In some studies, stroke mortality has been found to be higher in men, but differences are modified by age and higher rates are seen in women over the age of 85 years.[6] Stroke mortality is also higher among patients with lower socioeconomic status.[9, 11] Stroke is the somatic condition that leads to the most serious and long-term disabilities in adults and claims the most bed-days in Swedish hospitals.[12] Common problems after stroke are hemiplegia/hemiparesis, aphasia, poor balance, emotionalism, fatigue, depression, vascular cognitive impairment and dementia. Symptoms vary between patients depending on what part of the brain is affected. Functional outcome and quality of life after stroke have been found to be worse in women, and the differences are not fully explained by women being older, having poorer pre-stroke condition, or having a higher prevalence of co-morbidities.[6] The evidence on socioeconomic differences in functional outcome is unclear.[11]

Because of the large number of patients and the often serious consequences of stroke, the cost of stroke to society is high. Stroke and its aftermath consume significant resources for acute health care, rehabilitation, nursing homes, and

home care service. The total cost of stroke to Swedish society has been estimated to be 18.3 billion SEK a year.[13]

Risk factors for stroke can be both individual or non-individual and modifiable or non-modifiable. Some risk factors change over an individual's lifetime and can be interactive and/or cumulative. Some classic risk factors for stroke are hypertension, diabetes, atrial fibrillation, smoking, and lack of physical activity. The risk factors are generally the same for men and women, but the prevalence of some risk factors differs.[6, 14] Hypertension is associated with the most stroke cases based on the large number of individuals affected, but it does not pose the highest risk on an individual level.[15] A newly published meta-analysis investigating sex differences in the associations between systolic blood pressure and cardiovascular disease found no differences between men and women in the association between systolic blood pressure and risk of stroke.[16] Socioeconomic factors and ethnicity also show associations with increased risk of stroke.[9] Studies show an inverse relationship between socioeconomic status and hypertension, smoking, diabetes and physical inactivity in developed countries.[11] In developing countries, the association has been the opposite but this is changing as increasing gross national products lead to higher risks in lower socioeconomic groups.[17]

Prevention

The cornerstones of both primary and secondary stroke preventive strategies include lifestyle changes such as smoking cessation, increased physical activity, weight loss, and decreased stress. Pharmacotherapy is used together with lifestyle changes in secondary prevention as well as when lifestyle changes are insufficient in primary prevention.

For secondary prevention of stroke, antihypertensive drugs are effective for both hemorrhagic and ischemic strokes. No absolute target level for blood pressure has been defined, but a decrease of 10/5 mmHg has been beneficial.[18] The PROGRESS study (The Perindopril Protection Against Recurrent Stroke Study) showed a 28% reduction in the risk of stroke in patients treated with angiotensin converting enzyme (ACE) inhibitors and diuretics compared to placebo.[19] The association between blood pressure and risk of stroke was log linear for patients both with and without hypertension. A systematic review of randomised clinical trials found that lowering blood pressure was associated with a significant reduction in stroke incidence and total vascular events.[20] Beta-blockers, calcium channel blockers, diuretics, and ACE-inhibitors/Angiotensin-2 antagonists (ARB) are used and more than one substance is often needed for effective treatment.

For ischemic strokes, both statins and antithrombotic drugs are effective in preventing recurrent strokes. Statins (HMG-CoA reductase inhibitors) are the main

drug class used for lowering blood lipids and treating atherosclerosis. The Heart Protection Study (HPS) showed a 24% reduction in vascular events and a 25% reduction in stroke incidence with simvastatin treatment compared with placebo in high-risk individuals irrespective of initial blood lipid level.[21] In the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) study, treatment with atorvastatin decreased the risk of stroke by 16% as well as the risk of major cardiovascular events in stroke patients without coronary heart disease in comparison with placebo.[22] Secondary analyses from SPARCL showed no differences in effect between men and women.[23] A meta-analysis of randomised controlled trials (RCTs) on the effect of statins after stroke showed a pooled relative risk for recurrent stroke of 0.84 and 0.88 for all-cause mortality, without differences in effect between patient groups.[24]

Antiplatelet drugs such as acetylsalicylic acid (ASA), dipyridamole, and clopidogrel are used to prevent ischemic stroke in patients with non-cardioembolic disease. A meta-analysis of the effect of antiplatelet treatment on all vascular events shows an odds reduction of 22%.[25] Results from ESPRIT (European/Australasian Stroke Prevention in Reversible Ischaemia Trial) showed that combining ASA with dipyridamol is more effective than ASA alone.[26] In CAPRIE, clopidogrel had a slightly better effect than ASA on all patients with atherosclerotic vascular disease but the same effect in secondary prevention after stroke.[27] Warfarin is no better than ASA or placebo in patients without cardioemboli but increases the risk of bleeding.[28] There are some studies showing poorer effect of ASA in women compared to men[29, 30], but a meta-analysis found no significant difference in effect.[31]

Patients with atrial fibrillation and risk of thromboembolism (classified according to CHA2DS2-VASc risk scores) are best treated with anticoagulants to prevent ischemic strokes. In a Cochrane Review comparing the effect of anticoagulants with placebo, the odds ratio (OR) for recurrent stroke was 0.36 for the anticoagulant group.[32] Comparing secondary preventive effect of anticoagulants with antiplatelet drugs showed better effect for anticoagulants on both all vascular events (OR = 0.67) and on stroke (OR = 0.49).[33] Warfarin is effective for secondary prevention of stroke in both men and women[34], and no differences in the risk of bleeding have been found.[35]

National guidelines for stroke prevention

National guidelines are developed to support decisions about priorities in health care. The Swedish guidelines for stroke care support the use of the best treatments for stroke care and strive to ensure that all patients are treated equally irrespective of where they live. The national guidelines for stroke care have been updated, and the versions from 2005 and 2009 are of interest to this thesis.[36, 37]

The guidelines include recommendations for such things as acute care, rehabilitation, and primary and secondary prevention. The following drugs are recommended for the secondary prevention of stroke.

After ischemic or hemorragic stroke:

- Antihypertensive treatment with ACE-inhibitors or ARB, diuretics, beta-blockers, or calcium channel blockers.

After ischemic stroke

- Lipid-lowering treatment with statins
- Antiplatelet treatment with ASA, ASA + dipyridamole, or clopidogrel

After ischemic stroke, with atrial fibrillation

- Anticoagulant treatment

Recommendations on drug treatments for secondary prevention are mainly the same in both versions of the national guidelines. However, statins are given higher priority in 2009 compared to 2005, and new anticoagulants have been introduced in a 2011 complement to the 2009 guidelines.[38]

The Swedish national guidelines for secondary preventive drug treatment do not differentiate between men and women or different ethnic and socioeconomic groups.[36, 37] According to the guidelines, all treatments should be based on individual circumstances and although the premises can be different in different patient groups, e.g. women patients tend to be older than men, men and women should in general be treated equally.

Quality indicators for good stroke care have been developed alongside the development of the national guidelines. These indicators are based on scientific evidence and the consensus of medical professionals, health care providers, and patient representatives.[39] The quality indicators for use of drugs after stroke are[36]:

- *Indicator:* Treatment with antihypertensive medicines.
  Measured as: Proportion of patients with stroke with antihypertensive treatment at a) discharge from acute care and b) one year after stroke.
- *Indicator:* Warfarin treatment in atrial fibrillation after stroke.
  Measured as: Proportion of patients with warfarin treatment at a) discharge from acute care after brain infarction among those with atrial fibrillation b) 3-6 months after brain infarction among those with atrial fibrillation.
- *Indicator:* Statin treatment after brain infarction.
  Measured as: Proportion of patients with statin treatment at a) discharge after brain infarction b) one year after discharge from acute care.

Equality in Swedish health care

Health is not equally distributed in society. For stroke, the risk differs between different groups of patients (see above). Many factors, both individual and non-individual as well as health care-related and non-health care-related factors affect public health. The health care system cannot solve the problem of unequal distribution of health, but it should not increase the differences. The goal of health care in Sweden is, according to the Swedish Health and Medical Service Act of 1982, a good health and care on equal conditions to the entire population. Health care should be given with respect for every individual's equal value, and those with the greatest needs should be given highest priority.[40] According to Sweden's first national drug strategy from 2011, equal health care in the use of drugs is one of five long-term goals for accomplishing the vision of right medication for the benefit of patients and society.[41]

The Swedish Association of Local Authorities and Regions has published two reviews investigating whether health care in Sweden really is provided on equal terms in relation to sex and social differences (including immigration background).[42, 43] Results from both reports show that health care in Sweden is not always provided equally to all groups in society, and differences are more often in disadvantage to women and socially deprived groups. The data in those reviews, however, is from many different types of health problems and health care settings of varying magnitude and only cover parts of the Swedish health care system. It is, therefore, difficult to conclude that the Swedish system is unequal in general.

There are differences in the use of drugs between men and women and between different social groups. Women generally use more drugs then men except among children and the oldest age groups.[44] Higher rates in younger women are partly explained by the use of contraceptives. The fact that women seek health care more often is another reason why women tend to use more drugs, but data also show that women are more often prescribed drugs at medical appointments. Individuals with a lower level of education use more drugs compared to those with a higher education level[45], although there is a lower tendency to seek health care in lower socioeconomic status groups.[46, 47] The differences in use of drugs correspond mostly with the higher incidence and prevalence of disease among groups with lower socioeconomic status, and thus represents drug use according to needs.[45]

Although some differences are based on different disease patterns or risk factor patterns, other differences have been more difficult to explain and some even show inverse relationships to disease or risk. One example is dementia drugs that are more often used among patients with a higher education even though dementia is more common in the group with lower education.[48] In a study of the total population older than 20 years of age in one Swedish county, differences in

the use of all prescription drugs in regards to age, sex, and socioeconomic status were controlled for multi-morbidity.[49] The results of that study showed that the odds of men using prescription drugs were less than half of the odds of women. After controlling for multi-morbidity, the use of prescription drugs was lowest in the groups with the highest education level as well as in the group with the lowest income.

Differences in use of new technologies or new treatments can be most prominent during the initial phase of their use.[50] Secondary preventive drug treatment is not new, and all drugs or drug classes used at the time of these studies were well established on the market. Most groups of drugs included some generic drugs with a lower price.

Prescribing of drugs

Drug treatment is the most common intervention within health care, and drugs represent a large proportion of health care costs. In 2012, 6 387 894 Swedish citizens (67.4% of the total population) filled 102 539 830 prescriptions in Swedish pharmacies at a value of 25.3 billion SEK.[51]

All drugs used for prevention of stroke are prescription only drugs.

The WHO has defined rational use of medicines:

> *"Patients receive medication appropriate to their medical needs, in doses meeting their own individual requirements, for an adequate period of time and at the lowest costs to them and to the community."*[52]

More practically oriented recommendations have been developed for prescribers. One example is the "Ten Principles of Good Prescribing" developed by the British Pharmacological Society.[53]

1. Be clear about the reasons for prescribing
2. Take into account the patient's medication history before prescribing
3. Take into account other factors that might alter the benefits and risks of treatment
4. Take into account the patient's ideas, concerns, and expectations
5. Select effective, safe, and cost-effective medicines individualised for the patient
6. Adhere to national guidelines and local formularies where appropriate
7. Write unambiguous legal prescriptions using the correct documentation
8. Monitor the beneficial and adverse effects of medicines

9. Communicate and document prescribing decisions and the reasons for them
10. Prescribe within the limitations of your knowledge, skills and experience

Adherence is often discussed in relation to patients – whether patients actually use their prescribed drugs as intended – but adherence is sometimes also the matter of prescriber adherence to guidelines or recommendations. Guidelines and recommendations on prescribing drugs for specific diseases are based on population data. Every patient should not be prescribed drugs exactly according to national guidelines or recommendations, but a more general adherence to guidelines is important to promote evidence-based use of drugs. Prescribers do not always adhere to guidelines or keep updated about best treatment practice. A qualitative study on general practitioners' reasons for not prescribing lipid-lowering medication to diabetic patients shows both valid reasons for not following guidelines (previous side-effects, short life expectancy) but also reasons such as poor prescriber and/or patient motivation.[54] Studies also indicate that social structures have an impact on clinical decisions and adherence to guidelines.[55] Individual prescribing habits have been shown to be stable, and changing habits is a slow process that is the result of many different influences.[56]

Patient adherence to prescribed treatment

Rational prescribing of drugs is important for optimal health outcomes, but patients' participation in adhering to treatment is crucial. Patients' adherence to treatment has, however, been shown to vary considerably between patients, drugs, conditions, and over time.[57] A significant amount of research has gone into understanding how patients actually use their prescribed drugs and why they use them as they do. The results of these studies, however, have not been consistent, and lasting improvements in patient practice have been hard to accomplish.

In 2003, the WHO defined adherence as "*the extent to which a person's behaviour – taking medicines, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider*"[57]. According to the WHO, the word "agree" is important and differentiates adherence from the previously more used term "compliance". This change in wording is meant to reflect the more patient-centred health care that has developed in recent years, but a group within ISPOR (International Society for Pharmcoeconomics and Outcomes Research) have found that these terms are still used interchangeably in the literature.[58] Many different terms have been used over the years, such as compliance, adherence, persistence, and discontinuation.[59] They are all meant to reflect how patients use the drugs that are recommended to them. Unfortunately, expressions have been used in different ways and this has created a confusing

vocabulary in the field. According to the previously mentioned ISPOR report, adherence and compliance are used interchangeably and measure proportions of doses administered correctly during a specific time period (the intensity of treatment). Persistence, on the other hand, is a measure of time or duration. Others argue that measuring persistence of treatment should include both the intensity and duration of treatment.[60]

Non-adherence or poor adherence can be categorised as follows:[61]

- Patients do not accept the treatment and do not use it.
- Patients accept the treatment and continue to use it but not according to instructions. Patients might take an incorrect dose, take the medicine at the wrong times, or forget one or more doses occasionally.
- Patients accept the treatment and use it according to instructions but for a shorter time period than recommended.
- Patients accept the treatment but do not use it according to instructions and only use it for a shorter time period than recommended.

Another expression used in relation to patients' use of drugs is concordance. Concordance is not a measure of behaviour like adherence or persistence but reflects the process between the prescriber and the patient in trying to come to an understanding and agreement of the treatment prescribed or not prescribed.[62] Concordance reflects a more patient-centred type of care. Patient-centred care involves patients and relatives in planning health care with agreed-upon goals and strategies that are based on the patient's own experiences with their illness and their life in general.[63] In patient-centred care, the patient is no longer a passive recipient of experts' decisions.

The field of research on how patients use drugs is rather new. The problem was first recognised in the 1950s when some doctors realised that there was a problem with poor use of anti-tubercular drugs. From 1961 to 1974, only 245 articles were published on compliance.[64] In many of the earlier studies, the focus was on patients following medical advice given by someone else, an expert.[59] This view was later called paternalistic, and assuming a compliant patient to be rational or "good" and a non-compliant patient to be troublesome or "bad".[64, 65]

Importance and effect of adherence

The importance of adherence and the effect of non-adherence differ for different drugs and treatments. For example, one missed contraceptive pill can lead to a pregnancy while adherence to antibiotics is important to prevent drug resistance. Adherence is very important for the effects of drugs with a narrow therapeutic

window. One example from stroke prevention is warfarin. With too low of a concentration of warfarin in the blood, there is no or poor effect but too high a concentration increases the risk of bleeding. Other stroke preventive drugs are not as sensitive as warfarin in terms of therapeutic index, but a review of 41 studies on the outcome of adherence to drugs for hypertension and dyslipidemia shows a relation between positive outcome and adherence in the majority of studies (73%).[66] A study from the Netherlands showed a 28% increased risk of stroke after early discontinuation of antihypertensive drugs for primary prevention.[67] In another study, patients with high adherence to antihypertensive treatment had significantly higher odds of achieving blood pressure control compared to medium- or low-adherence patients.[68] In a review of 19 studies on the effect of adherence to statin treatment, the results showed that higher adherence decreased the risk of cardiovascular events and all-cause mortality in both primary and secondary prevention.[69] In stroke patients who were prescribed statins at discharge, discontinuation of treatment was associated with increased all-cause mortality (hazard ratio = 2.78; p = 0.003).[70] There is also some evidence that stopping statin treatment in acute stroke is harmful. In an RCT, withdrawal of statin treatment was associated with increased risk of death and dependency 3 months after stroke.[71] In a study from the US, persistence with antiplatelet drugs (ASA/dipyridamole or clopidogrel) in ischemic stroke patients was shown to be associated with decreased risk of recurrent strokes.[72]

In long-term treatments, adherence is more difficult than in a short course and preventive treatment is especially difficult.[57] The problem with adherence in prevention is thought to be because of the uncertainty of individual effect and the fact there is often lack of symptoms.

Some argue that the effect of adherence to drug treatment is difficult to measure because of the "healthy adherer effect". This suggests that adherence to drug treatment might be an indicator of healthy behaviour in general. In support of this, studies have shown that adherence to placebo is also associated with decreased mortality.[73]

Quantifying adherence

To be able to discuss the magnitude of poor adherence or the effect of interventions to improve adherence, it is necessary to be able to quantify adherence. There is, however, no single gold-standard method to measure adherence. Citing Professor Alan J. Christensen:

> *"From an assessment perspective, patient adherence has proven to be an extremely elusive phenomenon to capture. Adherence is a behavioral process, but direct behavioral measures of the process (for example, actual observation of regimen-related behavior) are generally impractical and are seldom used."*[74]

The two aspects of adherence that can be measured are intensity and duration of treatment. Intensity of treatment can be calculated as the degree (%) of adherence, but the degree of adherence can also be dichotomised through a cut-off between patients classified as adherent and non-adherent. Duration of treatment can be measured as the time of continuous treatment or as the proportion of patients on treatment during a specific time period.[58]

Some common methods to measure adherence are presented in Table 1.[75] The choice of method is based on the purpose of the measurement as well as what is possible from a practical standpoint. In a clinical setting or in a pharmacy, asking the patient (self-reporting) is easy and common. For an RCT, several methods could be used at the same time – such as self-reporting, tablet counting, and electronic monitoring – to both insure the best adherence possible and to have a good estimation of adherence. In large observational studies, registers of prescribed drugs or filled prescriptions are often used to estimate patients' use of drugs. Estimating use of drugs and patient adherence from data on filled prescriptions has become more common with the development of automated databases with data on individual level.

Table 1. Common methods to measure adherence or persistence.

Method	**Positive aspect**	**Negative aspect**	**Suitable use of the method**
Measure drug and/or drug metabolites in biological fluids	It is possible to determine if the person has used the drug or not	Requires repeated analyses of both drug and metabolites to evaluate when and how much of the drug has been used	- Few patients in a clinical setting - Clinical trial
Directly observed therapy (DOT)	It is possible to determine if the patient is not using the drug	- Impractical (especially in out-patient situations) - Not absolutely certain, the patient could pretend to swallow the drug	Few single patients in a clinical setting
Self-reporting (diaries, interviews, standardised questionnaires)	Simple to use and relatively low cost	Answers depend on how the questions are formulated and posed, and people sometimes overestimate their own adherence	- Patient in a clinical setting or pharmacy - Clinical trial (experimental studies) - Observational studies

Tablet counting	Simple to use and relatively low cost	- It is possible to remove tablets to hide non-adherence - It is only possible to calculate a proportion of a total amount	Clinical trial (experimental studies)
Electronic monitoring devices	- It is possible to follow dosing - It is possible to identify intentional non-adherence	- The patient might open the device without taking a dose. - The patient could be stressed about being ”under surveillance” - The results might not represent adherence under normal circumstances - Expensive	Clinical trial (experimental studies)
Control of filled prescriptions (often through automated registers)	- It is possible to determine if the patient stops treatment - Long intervals between filling of prescriptions suggests that drugs are probably not being used according to instructions - Relatively easy with computerised registers	Does not measure actual use of drugs but sales of drugs	- Pharmacoepidemiology (observational studies) - Large populations and real-life settings

Patient-reported adherence, both through questionnaires and interviews, is sometimes expected to result in overestimations of adherence due to self-presentation and patients forgetting about non-adherence. A meta-analysis found slightly, but not significantly, higher levels of adherence in nine studies comparing self-reporting with other measures[76], but self-reporting has also been found to predict future adherence.[77] Those individuals who self-report poor adherence are usually correct.

In wealthier countries, adherence to long-term treatment has been estimated to average 50%[57], but it is difficult to put an exact number on a general level of adherence. There are also differences in what is considered non-adherence, for example, patients can stop the treatment completely, take a long break from treatment (a "drug holiday"), modify the dose, or forget occasional doses. The many different definitions of adherence used, the different follow-up times, and the different measures of adherence make it difficult to give an exact number on adherence or to compare results from different studies.

Associated factors

Poor patient adherence is a complex problem, and reasons for non-adherence are diverse. Identifying factors associated with adherence is important to understand why poor adherence is so common, to possibly identify patients at highest risk, and ultimately to find out what can be done to prevent this problem. This has been the goal for many researchers and many factors have been tested for associations, but the results have sometimes been inconsistent (Table 2).[78] Some of the factors that have shown more consistent associations to adherence are therapy-related factors such as simple dosage regimens and non-invasive routes of administration; health care system-related factors such as accessibility of care and satisfaction with care; costs to patients; and disease-related factors where chronic conditions and an absence of symptoms are associated with poorer adherence.[78] Many studies are cross-sectional and this prevents drawing conclusions on causal relations.

Table 2. Factors tested for associations to adherence.[78]

Patient-centred factors
- Demographics: Age, sex, ethnicity, education, and marital status
- Psychological factors: personal beliefs and motivation
- Patient-prescriber relationship
- Health literacy
- Patient knowledge
- Other: smoking, use of alcohol, forgetfulness
Therapy-related factors
- Route of administration
- Treatment complexity
- Duration of treatment period
- Medication side effects
- Degree of behavioural change required
Social and economic factors
- Cost of therapy and income
- Social support
Health system factors
- Availability, accessibility, and satisfaction
Disease factors
- Disease severity, fluctuations, or absence of symptoms

Patients' beliefs that the use of drugs is important for their future health as well as their concerns about possible negative effects have been shown to be associated with adherence to treatment.[79-81] Many different theoretical psychological models have been developed to explain health-related behaviours. Howard Leventhal and colleagues have developed the Self-Regulatory Model (SRM) to explain how cognitions, motivations, and behaviours interact.[82] This is one of the models most often discussed in relation to patient adherence. Adherence to treatment is a health-related behaviour. Behaviour has an important impact on health through biological changes, through engaging (or avoiding) health risks, and through seeking care for early detection and treatment of disease.[83] Behaviour to maintain, restore, or improve health or prevent disease is often called health behaviour or health-related behaviour. Behaviour is genetically, culturally, socially, and emotionally influenced, and behaviour can sometimes seem irrational. Studies have shown that demographic and biomedical factors are not sufficient to explain adherence behaviour.[78]

Objectives

The overall aim of this thesis was to study the use of secondary preventive drugs after stroke among Swedish stroke patients.

The specific objectives were to study:

- inequalities in implementation of secondary preventive drug treatment in clinical practice
- patient adherence to treatment over time and factors related to adherence with treatment

Methods

Real-life data has been used to study the use of drugs in terms of prescribing of drugs and patient adherence to the prescribed drug treatments. For the different studies included in this thesis, register data has been used when available including clinical data, demographics, prescribed drugs, filling of prescriptions, co-morbidities, and socioeconomic status. For patients' beliefs or perceptions, register data was not available and this required a survey to a sample of patients.

Definitions

This thesis concerns the use of secondary preventive drugs after stroke both in terms of prescribing of drugs and how the patients use them. Many different expressions have been used in the field to describe how patients use prescribed drugs including "compliance", "adherence", "persistence", and "continuous use". Although the terminology in the field is confusing, most experts would agree that there are different aspects to how drugs are handled and that different expressions are often used for different aspects. However, for the readability of this thesis the expression "adherence" has been used in the cover story (except in definitions of outcome measures, in statistical methods, and in discussing other published studies) although other expressions have been used, and more than one aspect of how patients use drugs have been estimated in the original papers of this thesis.

Data sources

The data sources for this thesis include three national registers and databases as well as a questionnaire survey.

Registers and database

Riks-Stroke is the Swedish national quality register for stroke care.[84] A quality register in Sweden is defined as follows:

> *"A national quality registry contains individualised data concerning patient problems, medical interventions, and outcomes after treatment; within all healthcare production. It is annually monitored and approved for financial support by an Executive Committee."*[85]

The main aims of Riks-Stroke are to monitor and improve the quality of stroke care in the whole country and to follow-up on the national guidelines for stroke care, but the register is also used in research. Participation in a quality register such as Riks-Stroke is always voluntary, and registering a patient in a quality register requires patient consent.

In the acute phase of a stroke, data are collected by hospital staff and at 3 months and 12 months after stroke through patient questionnaires. Information from the acute phase includes such things as acute hospital treatments, stroke unit care, dependency in Activities of Daily Living (ADL) before stroke, risk factors, complications, plans for rehabilitation, and plans for return visits. Data from the 3-month follow-up questionnaire includes living conditions, dependency in ADL, return visits, self-rated health and depression, and information about the need for and the satisfaction with help and support, and rehabilitation. The 12-month questionnaire has not been used in this thesis. Data on preventive drugs used before stroke and prescribing of drugs at discharge from hospital are also available in the stroke register. Data on drugs consist mostly of data on groups of drugs, for example, beta-blockers, diuretics, ACE-inhibitors, ARBs, calcium antagonists, and statins. Antithrombotic drugs are reported on the substance level, including ASA, clopidogrel, dipyridamole, and warfarin. Stroke prevention was not an indication for the newer anticoagulants (dabigatran, rivaroxaban, and apixaban) at the time of these studies.

The Swedish Prescribed Drug Register is a national health data register managed by the National Board of Health and Welfare.[86, 87] National health data registers are regulated by law and participation is not optional for individuals.[88] The Prescribed Drug Register contains individualised information on all prescription drugs sold in all Swedish pharmacies since July 1, 2005. Coverage is over 99%. Information available in the register includes item and amount dispensed, the profession and practice of the prescriber, date of prescribing and dispensing, and information about the patient (age, sex, and residence). Data from the register can only be used for research, epidemiological studies, and statistics. Data were linked through the Swedish personal identification number. Drugs in the register are classified according to the Anatomical Therapeutic Chemical (ATC) Classification System. This makes analyses possible on both individual substances and on groups of drugs.

The Longitudinal integration database for health insurance and labour market studies (LISA by its Swedish acronym) from Statistics Sweden was used for information on socioeconomic status as indicated by income and highest level of education, and country of birth.[89] LISA contains information about individuals with links to families, companies, and places of employments and the data are updated yearly. Data on the individual level include employment, income, compensations, country of birth, latest year of immigration, and highest level of education. Data were linked through the Swedish personal identification number.

Survey

For information about patients' perceptions about stroke and beliefs about medicine, a survey including questions from BMQ (Beliefs about Medicines

Questionnaire), MARS (Medication Adherence Report Scale), and Brief IPQ (Brief Illness Perception Questionnaire), all validated questionnaires, were sent to a sample of stroke patients (tested translations[90]).

The main outcome in the survey was self-reported patient adherence, and the five-question version of MARS was used to estimate adherence.[91] The rationale for using MARS-5 was that it has been used in many different conditions and diseases and because of the Likert-type responses that it uses. On the five MARS statements about non-adherent behaviour, it is possible to answer ”Always”, “Often”, ”Sometimes”, ”Rarely”, or “Never” compared to other questionnaires where it is only possible to answer “Yes” or “No”. A total MARS score is calculated from the answers (1 = *always*, 2 = *often*, 3 = *sometimes*, 4 = *rarely*, and 5 = *never*). The total score has previously been used both as a continuous variable[92, 93] and with a cut-off for non-adherence.[94, 95]

From the identification of common beliefs about medicines in the literature and in interviews, Professor Rob Horne and colleagues developed a questionnaire to be able to assess patients' beliefs about medicines in a more quantitative way.[96, 97] The BMQ consists of two parts called BMQ-General and BMQ-Specific. BMQ-General assesses beliefs about medicines in general, and can thus also be used with individuals who do not themselves use any medicines. BMQ-Specific, on the other hand, asks questions about medicines used by the patient at the time of the survey. The BMQ-Specific consists of two subscales (Necessity and Concern) with five questions in each, and the BMQ-General consists of three subscales (Harm, Overuse, and Benefit) with four questions each. All questions are answered on a Likert-type scale with the alternatives “Strongly agree”, “Agree”, “Uncertain”, “Disagree”, and “Strongly disagree”. A total score is calculated for each subscale where 1 = strongly disagree and 5 = strongly agree.

The Brief IPQ is a short version of the Illness Perception Questionnaire-Revised (IPQ-R), which consists of more than 80 questions.[98] The shorter version contains nine questions and is intended to be used for very ill or elderly patients, if many other questions are being posed, or if the questionnaire will be answered several times by the same patients. The first eight questions in the questionnaire are answered on a scale from 0 to 10. The last question, a question about the most likely causes of the stroke as perceived by the patient, was not used because of difficulties in including answers from an open-ended question in the analysis. This questionnaire assesses patients' perceptions about their disease or condition. Questions were modified to be more specific to stroke based on suggestions from the developer of the questionnaire.

The survey questionnaire used in this thesis is shown in Appendix 1.

Data acquisition and sampling

Stroke patients were sampled from Riks-Stroke based on date of stroke onset and diagnosis (ICD-10 code).

Date of stroke onset:

- Paper I: 1 September 2005 – 31 August 2006
- Paper II: 1 July 2005 – 30 June 2006
- Paper III: 1 April 2004 – 31 December 2009
- Paper IV: 15 December 2011 – 15 March 2012. For the questionnaire survey, all patients who had a stroke within the timeframe were included if they were treated in a hospital that participated in our study and were discharged from the hospital to their own home.

ICD-10 codes:

- Paper I: ICD-10 I61 (Intracerebral haemorrhages), ICD-10 I63 (ischemic stroke), and ICD-10 I64 (strokes not specified as haemorrhage or infarction)
- Paper II: ICD-10 I63
- Paper III: ICD-10 I63
- Paper IV: ICD-10 I61, ICD-10 I63, and ICD-10 I64

Cross-linkage between registers was possible through the Swedish personal identification number used in all registers.

The study questionnaire for Paper IV was sent together with the 3-month follow-up questionnaire from Riks-Stroke. The Riks-Stroke contact persons at each participating hospital sent both questionnaires in the same envelope. All 74 hospitals participating in Riks-Stroke were invited to participate in the survey, and 25 volunteered. Thus sampling of hospitals was not random, but participating hospitals represent different geographical parts of the country (including 15 of 21 counties/regions in Sweden), both urban and rural areas, and different types of hospitals (University hospitals n = 4, large non-university hospitals n = 11, and community hospitals n = 10).

Data quality

Riks-Stroke was established in 1994, and since 1998 all hospitals in Sweden admitting acute stroke patients are included. The coverage of Riks-Stroke is presented in Table 3. From 1996 to 2006, coverage was calculated as a comparison of the number of cases in the register to an estimation of 300 cases per 100 000 inhabitants. Since 2007, the number of first-time strokes registered in Riks-Stroke is

compared with the number of first-time strokes in routine statistics from Swedish hospitals reported in the National Patient Register (NPR) maintained by the National Board of Health and Welfare. In a validation study, stroke has been shown to be over-diagnosed in routine health care by about 6%[99], and this lead to an underestimation of the coverage of Riks-Stroke. The majority of patients missing in Riks-Stroke (compared to the NPR) had not experienced an acute stroke (i.e. they had a residual condition, transient ischemic attack, or had suffered a trauma), had died early, or had not been treated in a stroke unit.[100, 101]

Table 3. Estimated first-ever stroke coverage of Riks-Stroke 1996–2012.

Year	Coverage (%)
1996	53
1997	61
1998	71
1999	77
2000	74
2001	78
2002	83
2003	87
2004	89
2005	93
2006	90
2007	82.4*
2008	82.4*
2009	85.0*
2010	88.1*
2011	90.5*
2012	88.0*

*compared with the NPR

Some variables have problems with missing data, e.g. smoking. Despite high coverage and low rates of missing values for most variables, the missing data is likely to be systematic to some extent.

The Swedish Prescribed Drug Register contains individualised data on all filled prescriptions from all Swedish pharmacies since 1 July 2005. Less than 0.3% of all entries lack complete information about patient identity.[86] The data do not include non-prescription drugs or drugs used in inpatient care. There is no information on indication, and dosage instructions are only available as free-text. There is no data in the register on the number of days supplied.

The LISA database from Statistics Sweden contains information about the total Swedish population who were ≥ 16 years of age.[89] Data in LISA come from different national sources.

- Country of birth is included from the national register of the total population that is updated yearly.
- Level of education is from the education register. The register is updated yearly with information from schools and educational organisers in Sweden. Information about the education of immigrants is mainly collected through questionnaire surveys to new immigrants.
- Income information was derived from the register for income and taxations. This register includes all nationally registered individuals and is produced yearly through collection of administrative data from, for example, the tax authority, the Swedish Social Insurance Agency, and the Swedish Pensions Agency.

The LISA variable with the highest proportion of missing values (Paper III) was education with 15.2% of all individuals (108 950) missing this information. Of these, 91.6% (15 182) were 80 years of age or older. Country of birth was only missing for 393 (0.4 %) individuals and income for 599 (0.5 %).

The different questionnaires used in the survey have been previously validated but not specifically for stroke.[91, 96, 97, 102] Sampling of hospitals participating in the questionnaire survey was not random, but participating hospitals represent both urban and rural areas (15 out of 21 Swedish counties/regions are represented) as well as different types of hospitals (University hospitals n = 4, large non-university hospitals n = 11, and community hospitals n = 10). Questionnaires were sent to patients who were discharged from the hospital to live in their own home, and out of those 811 patients who were still living at home 3 months after stroke onset 578 (73.4 %) responded to the questionnaire. Non-responders had more often had a previous stroke, reported depression or poor general health, smoked, or were living alone.

Determination of use of drugs

Use of drug has in this thesis been measured both as prescribing of drugs and as patients' adherence to treatment. The main outcomes in the different papers were:

I. The proportion of persistent users over different time intervals after stroke onset

II. The proportion of patients with a prescription at discharge and the proportions of primary non-adherent and persistent users 2 years after stroke onset
III. The proportion of patients with a statin prescription at discharge
IV. The proportion of patients non-adherent to treatment (self-reported adherence) 3 months after stroke onset

Persistent use (Papers I and II) was defined as at least one filled prescription for a drug in every 4 months period. (A supplementary analysis was, after publication, performed on data from Paper I using 6-month periods). A drug was considered prescribed (Papers II and III) if it was registered in Riks-Stroke as "Drug at discharge = yes", and primary non-adherence (Paper II) was defined as no filled prescription for a drug within the first 4 months after discharge from the hospital. Self-reported non-adherence to treatment (Paper IV) was defined as a total MARS score of 5 to 22.

Statistical methods

In the statistical analyses performed for the papers as described below, the level of significance was set as 0.05. Correspondingly, 95% confidence intervals were used. Descriptive data were mainly presented as proportions. For Likert-type scales (Paper IV), data were presented as medians and interquartile ranges. IBM SPSS Statistics was used for all statistical analyses.

I. Associations between 24-month persistence to treatment and background and medical factors were tested with multiple logistic regression (stepwise backward variable removal with $p > 0.10$ as the removal criterion).
II. Sex differences in the use of drugs were tested with age-adjusted Poisson regression. Associations between use of drugs and other variables were tested with multiple Poisson regression. Missing data were handled using multiple imputation. Separate models were used for men and women.
III. Age-adjusted logistic regression was used for group comparisons in the prescribing of statins. Multiple logistic regression was used to simultaneously test the effects of several factors on the prescribing of statins at discharge. Two-way interaction terms with year of stroke onset were included to test for possible differences in the rate of dissemination between different patient groups.
IV. Chi-squared test was used to test for differences in background and medical factors between different patient groups. A non-parametric test (Mann–Whitney U-test) was used to test for differences in questionnaire data with answers on Likert-type scales (BMQ and Brief IPQ). Multivariable associations were tested with logistic regression after checking the

linearity assumption (BMQ and Brief IPQ). Spearman's correlation coefficient was used to test for correlations between the BMQ subscales. Internal consistency for questionnaires with summarized scores (BMQ subscales and MARS) was tested with Cronbach's alpha.

Ethics

The studies in this thesis were approved by the Ethical Review Board of Umeå University.

- Papers I and II: 4 September 2007, Reg. No. 07-118M including an addition on 4 June 2009
- Paper III: 2 October 2012, Reg. No. 2012-321-31M
- Paper IV: 17 January 2012, Reg. No. 2011-375-31M

Data in the national health registers is, according to law, under secrecy, but secrecy can be broken for research purposes. Data extraction involving living individuals from Riks-Stroke, the National Board for Health and Welfare, and Statistics Sweden require approval from an Ethical Review Board. Data was anonymous in the delivered file. The personal identification numbers had been removed. The main risk to individuals included in observational pharmacoepidemiological research is violation of confidentiality. Health-related data can be considered especially sensitive information, and because the national health data registers are not optional and patients do not give consent to participate, the responsibility for non-disclosure should be highlighted.

Participants in the questionnaire survey were given written information about confidentiality and data protection, that the study was voluntary and would not affect future care, and that they could withdraw consent at any time.

Results

Data from July 2005 to June 2006 on prescribed drugs at discharge from hospital after a stroke showed that 75% of all stroke patients were prescribed at least one antihypertensive drug. For patients with an ischemic stroke, 40% were discharged with a statin and of those without atrial fibrillation 82% were prescribed antiplatelet drugs. Results from Paper III showed that prescribing of statins has increased over time from 33% in 2004 to 60% in 2009. Of ischemic stroke patients with atrial fibrillation, 32% were discharged with prescriptions for warfarin in 2005.

Unpublished data from the 2005–2006 cohort showed the proportions of patients who filled a prescription for a preventive drug in the 4 months prior to stroke onset. Out of all patients, 61% had filled a prescription for any hypertensive drug within 4 months of their stroke, 18% and 43% of ischemic stroke patients had filled a prescription for a statin and some antiplatelet drug, respectively, and 14% of ischemic stroke patients with atrial fibrillation had filled a prescription for warfarin.

Inequalities in implementation of secondary preventive drug treatment in clinical practice

Sex

Our data on the prescribing of drugs for secondary prevention of stroke showed differences between men and women in the prescribing of statins and warfarin. A larger proportion of men were prescribed both statins and warfarin after stroke (Table 4). The comparison between men and women was age-adjusted. Differences between men and women in the prescribing of antihypertensive and antiplatelet drugs were not statistically significant.

Table 4. Age-adjusted comparison of the prescribing of secondary preventive drugs after stroke between men and women presented as prevalence ratios (PR) with 95% CI.

	Sex	Valid observ.	(%)	95% CI	Age-adjusted PR (95% CI)
Prescribing of					
Antihypertensive	Men	9 265	74.2	73.3–75.1	Reference
	Women	8 951	76.7	75.8–77.6	1.01 (0.97–1.04)
Statin*	Men	6 829	48.8	47.7–50.0	Reference
	Women	6 319	38.1	36.9–39.3	0.86 (0.82–0.91)
Antiplatelet	Men	9 271	81.3	80.5–82.1	Reference
	Women	8 953	82.6	81.9–83.4	1.02 (0.98–1.05)
Warfarin**	Men	2 352	38.4	36.4–40.4	Reference
	Women	2 532	26.4	24.7–28.1	0.88 (0.79–0.97)

Prescribing was analysed for all patients who were alive at discharge

*Only for patients without atrial fibrillation

**Only for patients with atrial fibrillation.

Associations with demographic, medical, and health care-related factors were tested in separate models for men and women to determine if different factors were associated with different prescribing for men and women. The results of this analysis showed that although prescribing was higher in men, mostly the same factors were associated with the prescribing of statin (Table 5). Age, institutional living, history of stroke, level of consciousness at admission, and having used the drug before stroke were associated with the prescribing of both warfarin and statins in both men and women. Stroke unit care and smoking in women were only associated with prescribing of statins, and diabetes in men was only associated with prescribing of warfarin.

Table 5. Factors tested for association with prescribing of statins and warfarin in men and women. ↑ indicates an association with a prevalence ratio (PR) and 95% CI > 1, and ↓ indicates a PR and 95% CI < 1.

	Statin prescribing		Warfarin prescribing	
	Men	Women	Men	Women
Higher age	↓	↓	↓	↓
Institutional living before stroke	↓	↓	↓	↓
History of stroke	↓	↓	↓	↓
Low level of consciousness at admission	↓	↓	↓	↓
Stroke unit care	↑	↑		
Smoking before stroke		↑		
Diabetes before stroke			↓	
Treatment with drug at stroke onset	↑	↑	↑	↑

Socioeconomic status

Inequalities in the prescribing of statins after ischemic stroke between groups with different socioeconomic status were tested in Paper III. When using disposable income and the highest level of education as proxies for socioeconomic status, the results showed inequalities in prescribing after controlling for demographic, medical, and socioeconomic differences (Table 6). Patients with a higher income and a higher level of education were more often prescribed a statin after stroke, but the difference between primary and secondary school levels decreased between 2004 and 2009.

Table 6. Proportion of patients with a statin prescription at discharge in subgroups of ischemic stroke patients from 2004 to 2009.

	Statin treatment		
	Valid observations	Proportion with a statin prescription (%)	Multiple logistic regression odds ratios (95% CI)
Education			
Primary school	47 263	48.0	Reference
Secondary school	31 786	55.7	1.07 (1.04–1.11)
University	12 550	57.3	1.05 (1.01–1.10)
Income			
Low	35 764	40.1	Reference
Medium	35 806	42.7	1.02 (0.99–1.06)
High	35 850	56.6	1.24 (1.19–1.28)
Country of birth			
Sweden	95 706	45.6	Reference
Nordic countries*	5 720	52.7	1.07 (1.01–1.14)
Europe†	4 399	54.9	1.31 (1.22–1.40)
Other countries	1800	54.8	1.20 (1.08–1.34)

*except Sweden

†except the Nordic countries

Multivariable analyses were adjusted for education, income, country of birth, year, age, sex, smoking, ADL dependency, history of stroke, atrial fibrillation, history of diabetes, antihypertensive medication at onset of stroke, and level of consciousness on admission.

Country of birth

For country of birth, the largest proportion with a statin prescription was those patients born outside the Nordic countries. After adjusting for patient-related factors, the odds of statin prescribing was still higher in patients born in Nordic countries, Europe, and countries outside of Europe compared to patients born in Sweden (Table 6). Prescribing to patients born in Europe increased from 2004 to 2009 compared to prescribing to patients born in Sweden. Differences in patient characteristics and risk factors between the different groups based on country of birth are presented in Table 7 (unpublished data). These differences were controlled for in the multivariable analysis.

Table 7. Patient characteristics and risk factors, presented as proportions, for patients born in Sweden, Nordic countries (excepting Sweden), Europe (excepting Nordic countries), and other countries (unpublished data).

	Sweden	Nordic countries	Europe	Other countries	*Total*
	n = 96 537 (%)	n = 5 772 (%)	n = 4 431 (%)	n = 1 817 (%)	*n = 108 557 (%)*
Sex					
Men	51.5	46.0	52.9	53.9	*51.3*
Women	48.5	54.0	47.1	46.1	*48.7*
Age group					
18–59	9.1	11.6	13.4	32.1	*9.8*
60–69	16.8	23.5	22.6	21.1	*17.5*
70–79	29.4	36.7	34.7	25.6	*29.9*
80+	44.7	28.2	29.2	21.1	*42.8*
Education					
Primary school	44.5	48.5	31.5	30.9	*43.9*
Secondary school	29.2	32.7	34.7	23.1	*29.5*
University	11.6	8.7	14.5	18.5	*11.7*
Income					
Low	32.5	38.1	39.0	50.5	*33.3*
Medium	33.6	31.4	31.5	29.2	*33.3*
High	33.9	30.5	29.5	20.3	*33.3*
Smoking					
No	76.5	67.7	72.3	69.6	*75.8*
Yes	13.3	22.0	18.0	20.1	*14.1*
Dependent in ADL					
No	90.1	92.2	92.3	91.1	*90.3*
Yes	9.9	7.8	7.7	8.9	*9.7*
Previous stroke					
No	73.6	73.1	73.8	75.7	*73.6*
Yes	26.4	26.9	26.2	24.3	*26.4*
Atrial fibrillation					
No	71.7	75.3	76.2	84.2	*72.3*
Yes	28.3	24.7	23.8	15.8	*27.7*
History of diabetes					
No	79.8	76.8	73.2	69.2	*79.2*
Yes	20.2	23.2	26.8	30.8	*20.8*
Antihypertensive medication					
No	42.2	41.2	43.7	47.2	*42.3*
Yes	57.8	58.8	56.3	52.8	*57.7*
Level of consciousness at admission					
Alert	89.6	89.5	90.2	89.7	*89.6*
Drowsy	8.8	8.8	8.3	8.7	*8.8*
Unconscious	1.6	1.7	1.5	1.6	*1.6*

Published results were not adjusted for a possible cluster effect from hospitals. Including hospitals in the analysis (Paper III) showed large differences between hospitals (OR between 0.4 and 8.0) but did not change associations between prescribing of statins and education, income, and country of birth except for university education, which was no longer significant (data not shown).

Patient adherence to treatment over time and factors related to adherence with treatment

Primary non-adherence to secondary preventive drug treatment after stroke was low in this sample of Swedish stroke patients. Most patients initially continued the preventive treatment that was initiated and prescribed in hospitals after a stroke (Paper II). The proportions of primary non-adherence were 4.4% for men and 4.2% for women for antihypertensive drugs, 7.4% for men and 7.9% for women for statins, 5.5% for both men and women for antiplatelets, and 10.3% for men and 11.4% for women for warfarin. The differences between men and women were not statistically significant.

Adherence to prescribed treatment, measured as the proportion of patients who continuously filled prescriptions at a pharmacy, decreased over time. Two years after their stroke, 74.2% of patients prescribed any antihypertensive drugs had been continuously filling prescriptions for some antihypertensive drug, 56.1% had been filling prescriptions for statins, 63.7% had been filling prescriptions for antiplatelet drugs, and 45.0% had been filling prescriptions for warfarin. Results for different types of antihypertensive drugs and different antiplatelet drugs are presented in Table 8.

Table 8. Proportion of adherent users among patients discharged from the hospital with prescriptions for different drugs.

	Patients discharged with respective drug and alive 24 months after discharge	Drug dispensed continuously for 24 months after discharge‡
		n (%)
Any antihypertensive drug	11 915	8 835 (74.2)
- Diuretics	5 383	3 168 (58.9)
- ACE inhibitor/ARB	6 283	3 537 (56.3)
- Beta-blockers	6 731	4 138 (61.5)
- Ca-inhibitors	3 502	1 949 (55.7)
Statins*	6 338	3 556 (56.1)
Any antiplatelet drug*	11 385	7 249 (63.7)
- ASA	10 684	6 576 (61.5)
- Dipyridamole	1 989	925 (46.5)

- Clopidogrel	894	352 (39.4)
Warfarin**	1 250	562 (45.0)

*Only for patients with ischemic stroke
**Only for patients with ischemic stroke and atrial fibrillation
‡ Data are shown for surviving stroke patients at 24 months.

Results from the supplementary analysis of the data in Paper I are presented in Table 9 (unpublished data). Using 6-month periods instead of 4 month increased the proportions of patients continuously filing prescriptions, but levels of drug use still decreased over time.

Table 9. Persistent users among patients discharged with prescriptions for different drugs. Persistent use is defined as at least one filled prescription for a drug in every 6-month period after discharge.

	At discharge[1]	1–6 months[1]	1–12 months[1]	1–18 months[1]	1–24 months[1]
Discharged with antihypertensive drug[2]	N=15 845	N=14 194	N=13 427	N=12 649	N=11 987
Persistent with antihypertensive drug[3]	n (%)	n (%) 13 809 (97.3)	n (%) 12 697 (94.6)	n (%) 11 684 (92.4)	n (%) 10 894 (90.9)
Discharged with statin[2]*	N=7 331	N=7 013	N=6 817	N=6 589	N=6398
Persistent with statin[3]	n (%)	n (%) 6 602 (94.1)	n (%) 5 884 (86.3)	n (%) 5 342 (81.1)	n (%) 4 954 (77.4)
Discharged with antiplatelet drug[2]*	N=14 869	N=13 410	N=12 700	N=12 021	N=11 388
Persistent with antiplatelet drug[3]	n (%)	n (%) 12 892 (96.1)	n (%) 11 422 (89.9)	n (%) 10 335 (86.0)	n (%) 9 477 (83.2)
Discharged with warfarin[2]**	N=1 529	N=1 446	N=1 399	N=1 338	N=1 271
Persistent with warfarin[3]	n (%)	n (%) 1 347 (93.2)	n (%) 1 163 (83.1)	n (%) 1 017 (76.0)	n (%) 897 (70.6)

[1] Patients alive at end of the time period
[2] According to Riks-Stroke.
[3] Drug dispensed at a pharmacy at least once in every 6-month period.
*Only for patients with ischemic stroke
**Only for patients with ischemic stroke and atrial fibrillation

In the questionnaire survey, 578 patients self-rated their general (not specific drugs) non-adherent behaviour 3 months after stroke using the MARS questionnaire. With dichotomised MARS scores (using a total score of 22 or lower as non-adherent), 12.5% of patients were classified as non-adherent. The numbers and proportions of patients who self-reported non-adherence (answered "sometimes"/"often"/"always") for each MARS statement are presented in Table 10.

Table 10. Numbers and proportions of patients self-reporting non-adherence (answered "sometimes"/"often"/"always") for each MARS statement.

MARS statement	Valid observations	Missing	Number (%) of patients who self-reported non-adherent behaviour
I forget to take my medicines	585	10	57 (9.7)
I alter the dose of my medicines	584	11	75 (12.8)
I stop taking my medicines for a while	583	12	13 (2.2)
I decide to miss out on a dose	581	14	49 (8.4)
I take less than instructed	583	12	26 (4.5)

Sex showed an association with refill adherence to antihypertensive drugs (Papers I and II) and antiplatelet drugs (Paper I) with women being more adherent. Adherence to drug treatment for most drugs was also associated with good self-rated health, living in institutions, and, for antihypertensive drugs and statins, with having used the drug before stroke. For statins and warfarin, a first-ever stroke was also associated with continuous use.

In the questionnaire survey, non-adherent behaviour was associated with both higher scores on negative personal beliefs about medicines (BMQ-Concern OR = 1.12, 95% CI 1.05–1.21, BMQ-Overuse OR = 1.29, 95% CI 1.14–1.45, and BMQ-Harm OR = 1.12, 95% CI 1.01–1.24) and with lower scores on positive beliefs about medicines (BMQ-Necessity OR = 0.90, 95% CI 0.83–0.98 and BMQ-Benefit OR = 0.77, 95% CI 0.68–0.87). Associations between adherence and illness perceptions were not statistically significant in this sample except for the one question about preventive treatment.

Discussion

Methodological considerations

Observational studies are the best options to capture everyday practice in average clinical settings. Data from experimental studies often overestimate adherence and do not reflect real-life situations.[103] Register data is, when available, both cheaper and faster to use compared to collecting new research data. Data on filled prescriptions is the type of register data most often used to estimate drug use in both national and international epidemiological studies. The main reason for this is that large registers or databases on prescribing are not as common as registers or administrative databases on filled prescriptions. In this case, data on drugs prescribed at discharge from the hospital were available in Riks-Stroke, which made a comparison between prescribed and purchased drugs possible. The registers and database used were all nationwide, and this made it possible to include large samples. Because of the high coverage of the registers and database used, selection is not likely to be a significant problem. The many national registers in Sweden are almost unique and, together with the personal identification number, give opportunities for large register-based studies and cross linkage between registers and databases.

The cross-sectional design of the studies in this thesis prevents conclusions from being drawn with regard to causality. It is a problem that most studies on adherence to treatment are cross-sectional.

Patients' adherence to treatment has proven difficult to measure. There is no perfect method and it is difficult to provide an exact value for adherence to treatment. Different definitions of adherence, different measurements, and different follow-up times often result in different estimates of adherence. Data on filled prescriptions, commonly used to estimate adherence in studies with large samples, were used in Papers I and II. The drug had to be bought at least once in every 4 month period for the patient to be considered adherent.

Many different measures of refill adherence have been used in the literature.[60, 104, 105] The measure used in Papers I and II only calculated the duration of treatment, not the intensity of treatment. A two-dimensional method, measuring both intensity and duration of treatment, should, according to Caetano et al., be used when the available data include a measurement of days supplied.[60] Data from the Swedish Prescribed Drug Register, however, do not include a measurement of days supplied. In Paper I, the proportions of adherent patients were calculated for different time intervals. The numbers of surviving patients in each time interval were considered, but an alternative method would have been to use survival

analysis.[59] With the method used in Papers I and II, it is possible to see that some patients do not continue treatment because they are not continuously buying the drug. It is also possible to investigate differences in adherence between groups because the method used is unlikely to differ between patient groups.

The Swedish system for reimbursement of drug cost does not allow patients to purchase drugs for more than 3 months at a time, and at least two thirds of the drugs should, according to dosage instructions on the prescriptions, be used before another filling of a prescription is allowed. This was the basis for choosing 4-month periods in our refill adherence model. Four months might be short, however, considering that many packages contain up to 100 tablets (slightly more than a 3-month supply) and that patients who purchase drugs as soon as they are allowed to (2 months after the last purchase) might be able to stockpile an amount that covers more than 4 months. A period of double the length of the prescriptions has been recommended in the literature.[106] A sensitivity analysis using 6 months instead of 4 months, therefore, was performed on the same data as Paper I. As expected, the longer time period gave higher levels of adherence, and this has also been shown in other studies comparing different methods for measuring adherence.[60, 106] Four-month periods might be too short to allow for smaller deviations in patients' use of drugs or for irregular filling of prescriptions without irregular use of the drugs.[106] Six-month periods on the other hand only require patients classified as adherent to fill two prescriptions a year (only 6 of 12 months would be covered). Because the purpose of the treatment is to prevent new strokes this seems low from a clinical point of view.

Using data on filled prescriptions to estimate patients' adherence to drug treatment is always a crude estimate. Not all drugs sold are used, and sales data do not reveal whether patients follow the dosage instructions. This might lead to misclassification of non-adherent patients as adherent. Patients who discontinue treatment after advice from medical staff might also be misclassified as non-adherent. Although the Swedish Prescribed Drug Register does not include a measure of days supplied, an assumption can be made that no more drugs than would last for 100 days are issued at a time. However, in practice this is often not true for warfarin. Because dose adjustments for warfarin are common, dosage instructions on prescriptions are often written as "According to specific instructions", and the number of tablets issued is usually calculated to cover possible increases in the dose. Our results on refill adherence to warfarin treatment should, therefore, be interpreted with caution. Patients using warfarin are also a highly monitored patient group, and this is likely to affect adherence to warfarin treatment.

In this thesis, adherence to treatment has been estimated with both register data (refill adherence) and questionnaire data (self-reported adherence), but the results

of these two methods have not been compared. The questionnaires were filled in 3 months after stroke onset, and because Swedish prescriptions often cover an amount of drug that will last for 3 months only patients who did not buy a drug at all within the first 3 months after a stroke would be classified as non-adherent according to register data. It would also be difficult to compare results because estimations using register data were calculated for every group of drugs, but with the questionnaire non-adherence was not specific for preventive drugs after stroke. Questions about non-adherent behaviours in the questionnaire were not specifically aimed at drugs used for the secondary prevention of stroke. This was deliberate because of the many possible indications for secondary preventive drugs and the possibility that patients do not always know that, for example, a drug that was prescribed many years ago for hypertension is also intended to prevent them from having another stroke even though they had a stroke while taking the drug.

Use of drugs has been measured both as prescribing of drugs and as adherence to treatment. Prescribing has been the easy outcome to measure because a drug was either prescribed or not according to the Riks-Stroke data. To measure adherence is to measure behaviour, how patients behave with their recommended drugs. It is difficult to measure behaviour, but it is also difficult to measure the process in prescribing and whether patients were included in the process (patient centeredness). It is possible to estimate patient behaviour if the prescription was more of an "order" and if the prescription was an agreement between the prescriber and the patient.

The NPR could have been used instead of the national quality register to identify stroke patients. This would have slightly increased the coverage of hospital-treated stroke patients and increased the possibility to include more co-morbidities in the analysis, but information on prescribed drugs and data from the 3-month follow-up questionnaire would not have been available. The 3-month follow-up includes patient-reported information about care and support, about dependency in ADL, and about self-rated health. A possible cluster effect in the Riks-Stroke data was examined in a supplementary analysis of the data on prescribing of statins in Paper III. Although prescribing differed between hospitals, these differences were not associated with differences in the patient characteristics investigated.

Common indicators of socioeconomic status are education, income, and occupation. We chose to only include highest level of education and disposable income from the LISA database because using occupation would have classified most patients as "retired". The correlation between education and income was low in our sample indicating that different aspects of socioeconomic status are captured using the education and income variables.

Findings and implications

Use of secondary preventive drugs after stroke

There is strong evidence in the literature supporting the use of drugs to prevent recurrent stroke, and both national and international guidelines on stroke prevention include the use of drugs.[18, 36] A large proportion of Swedish stroke patients were prescribed effective treatments for stroke prevention after their first-ever stroke, and the use of statins increased from 2004 to 2009. More recent data from the 2011 Riks-Stroke report show that 77% of all stroke patients are discharged with antihypertensive treatment, 64% with a prescription for a statin, and 81% are prescribed an antiplatelet drug.[107] The number of patients prescribed anticoagulants has increased since 2005, and the introduction of new anticoagulants could be one explanation for this increase. Riks-Stroke data on anticoagulants in 2011 were only given for patients younger than 80 years of age, and 64% of these patients with atrial fibrillation were prescribed anticoagulants. In total, 92% of ischemic stroke patients received some type of antithrombotic drug (anticoagulants or antiplatelets). The use of secondary preventive drugs after stroke is high in Sweden compared to international use.[108] In a large study, data from 17 countries showed that the use of effective secondary preventive drugs differs significantly between countries at different levels of economic development.[108] Patients from high-income countries, including Sweden, have the highest use of secondary preventive drugs.

The data on prescribing presented in this thesis are from prescriptions given at discharge from hospital, but some patients could have been prescribed secondary preventive drug treatment after discharge. Comparing the number of persons prescribed drugs at discharge with the number of patients who filled a prescription within 4 months of discharge showed, for most drugs, a higher number of patients with dispensed drugs compared to the number of patients with a prescription at discharge even though the number of patients alive at end of 4 months was lower (unpublished data).

Most patients initially continue the drug treatment that was initiated during their hospital admission. Stroke is commonly known to be a serious condition, and this might be one explanation for the high primary adherence to stroke preventive treatment.

Trends of decreasing use of drugs among patients followed for 2 years after a stroke is problematic because secondary preventive pharmacotherapy is usually considered a lifelong treatment. Treatment can, of course, be discontinued for medical reasons (e.g. adverse drug reactions, polypharmacy, drug interactions, benefits are not expected to balance risks, etc.), but the magnitude of this is not

likely to be large. In our results, we have not been able to distinguish between treatments interrupted by patients from those interrupted by the prescribers. Results from the Adherence eValuation After Ischemic stroke–Longitudinal (AVAIL) Registry from the US found that approximately one third of stroke patients discontinued preventive drug treatments (warfarin, antiplatelet, antihypertensive, lipid-lowering, and diabetes medications) within 12 months of discharge from the hospital.[109] AVAIL used interviews and asked patients about reasons for discontinuation and about who had decided about discontinuation. The most common reason for discontinuation was a recommendation by the health care provider. When only cases who admitted having ended treatment themselves, or did not specify who had decided, were included in the analysis, non-adherence was approximately 15%. Persistence to antiplatelet drug treatment after ischemic stroke has also been investigated in a Danish study using register data on filled prescriptions. After a median follow-up of 2.8 years, 36.0% of patients had discontinued treatment.[110] In a meta-analysis including over 370 000 patients from studies of refill adherence in prevention of cardiovascular disease, adherence at a median time of 24 months was estimated to be 57% (95% CI 50–64).[111] ASA, ACE-inhibitors, ARB, beta-blockers, calcium-channel blockers, thiazides, and statins were studied and adherence was higher in secondary compared to primary prevention.

Although there are many effective drugs and treatments available, they are not always utilised to their full potential. Both prescribing of drugs and adherence to treatment could improve the use of drugs in health care and society. It is, of course, important to develop new and better drugs, but it has been suggested that it could actually be more efficient to improve the use of drugs and treatments that are currently available.

Inequalities in use of drug

Few differences between men and women were found in the use of secondary preventive drugs. Men were prescribed statins and warfarin to a higher degree, and women continued antihypertensive (Papers I and II) and antiplatelet treatment (Paper I) more often. Previous studies on sex differences in the prescribing of drugs have shown varying results, but differences that have been found are more often to women's disadvantage.[112-114] Clinical practice might have improved in recent years after discussions about inequalities. A Danish study from 2010 found no sex-related differences in the use of drugs after stroke.[115]

Results from Paper III showed that patients with higher socioeconomic status were more likely to be prescribed statins at discharge. This is in accordance with two Swedish studies on secondary prevention after myocardial infarction.[116, 117] The data also showed that patients born outside of Sweden were more likely to be

prescribed statins compared with patients born in Sweden. This is contrary to results from a Swedish study on secondary preventive drug treatment after myocardial infarction.[116] Data in Table 7 show that the demographic and risk factor profiles differ between groups born in different countries. Although the analysis controlled for the differences presented in Table 7, differences in prescribing of statins remained. Socioeconomic differences in the prescribing of statins could not be explained with the available data. This would probably require more targeted data.

Two goals of the Swedish Health and Medical Service Act are to provide care under equal conditions to the entire population and to ensure that those with the greatest needs are given priority.[40] The national guidelines on stroke care are based on horizontal equality. Stroke-preventive drug treatment should, according to the national guidelines, be based on individual circumstances but general differences in recommendations are not made between men and women or between different social groups.[36, 37] Differences in use of drugs are thus not supported by the law or by national guidelines.

A recently published study on data from Riks-Stroke showed an association between low socioeconomic status and increased mortality, and the differences in mortality were not explained by differences in the prescribing of secondary preventive drugs after stroke.[118] Although differences in health or mortality are only partly caused by differences in health care, including use of drugs, patient groups with higher incidence and mortality should not be prescribed less preventive drugs. There is an association between health and socioeconomic status with better health in high socioeconomic groups.[119] Stroke incidence and mortality are, for example, higher in groups with lower socioeconomic status.[7, 8] In Sweden, women and individuals with lower socioeconomic status generally use more drugs compared to men and individuals with higher socioeconomic status.[44, 45] The differences are often, but not always, explained by differences in disease or risk factor patterns. Lower levels of preventive drug use among stroke patients with lower socioeconomic status are, therefore, problematic.

Previous studies have shown associations between prescribing of drugs and factors such as age, sex, education, income, therapeutic traditions, and health care practices.[45, 49, 120] Several of these factors are non-modifiable, and this indicates that it is prescribing practices that must change.

We have not considered possible differences within the country or inequalities in the use of newer and more expensive drugs. A report from the National Board of Health and Welfare from 2007 shows that men and patients with high socioeconomic status more often used newer and more expensive antiplatelet

drugs after stroke compared to women and groups with lower socioeconomic status.[121]

Factors associated with adherence to drug treatment

Most of the factors that we have tested for associations with use of drugs have been patient related such as age, sex, ethnicity, education, income, personal beliefs, smoking, and medical or health-related factors. However, we have also looked at treatment-related factors such as having used the drug before stroke; social support factors such as being dependent on help or support from relatives or being dissatisfied with support; and health care system-related factors such as dissatisfaction with care or having had a return visits. Our results on factors associated with adherence showed that patients living in institutions after stroke or those who self-reported good health were generally more adherent with treatment that was prescribed at discharge. Some factors were only associated with adherent use of certain drugs, for example, women were more adherent with antihypertensive drugs, and having used the drug before stroke increased the odds of being adherent with antihypertensive drugs and statins. Adherence was also more common among patients who had their first-ever stoke compared to those with recurrent stroke. Fewer associated factors were found in Paper II compared to Paper I. In Paper II, factors associated with adherence were analysed in separate models for men and women, and Poisson regression is also considered a more conservative method compared to logistic regression.

Paper IV showed that adherence to treatment in a sample of stroke patients was associated with patients' personal beliefs about medicines. Non-adherent patients scored higher on negative beliefs about medicines and lower on positive beliefs. This is consistent with findings from several other studies[81, 92] and is in line with theoretical models of health-related behaviour.[82] In our study, non-adherence to treatment was not strongly associated with patients' perceptions about stroke. According to the SRM, symptoms and sensations are interpreted by patients as representations of an illness and help them to take action and cope with disease. Coping efforts are appraised and monitored and might change how the illness is viewed or alter the coping process.[82] In our study, representations of illness, as measured on the Brief IPQ, were not associated with coping in terms of self-reported adherence to preventive treatment. Stronger associations between beliefs about medicines and adherence than between illness perceptions and adherence have also been found in previous studies.[79, 80, 92] An extended version of the SRM proposes that illness perceptions are often associated with adherence indirectly through beliefs about medicines that are associated with illness perceptions.[93] We have not tested the full extended model, but our results showed stronger relations between beliefs about medicines and adherence than between illness perceptions and adherence.

It has been hard to find consistent evidence of factors associated with adherence in the literature.[78] One explanation for this might be interactions between factors, but such interactions have not been widely studied. Patient adherence to treatment is a very complex process and is not explained by single factors.[74] In the same way that the biomedical model has proven insufficient to fully explain the development of health and diseases, adherence or poor adherence is not explained by just demographic or medical factors. The biopsychosocial model is often used to understand how biological, psychological, and social factors can cause disease, influence patients' understanding of a disease, and affect the outcome of disease.[122] Adherence to treatment is likely affected in the same way by biological, psychological and social factors. Studies show that both patients' perceptions about disease and disease severity[123] as well as social and cultural factors[74] affect the behaviour of patients in adhering to treatment. A biopsychosocial model is a very complex model, and it is impossible to test a "full" model. In the papers of this thesis, we have tried to include different factors of medical, psychological, and social origin that could be associated with the use of drugs.

Working on improving long-term adherence

Stroke is a serious condition that affects many individuals. Strokes often lead to long-term disability and suffering for those afflicted and are a significant burden on society. Not all strokes can be prevented, but rational use of available drugs could prevent many. The evidence for the benefits of secondary preventive drug treatment after stroke is convincing, and this might make it seem that effective drug prevention should be easy to accomplish. A significant amount of time and research has been put into understanding and improving the use of drugs, but suboptimal use of stroke-preventive drugs is still a public health problem. The results presented in this thesis show that most stroke patients use their prescribed preventive drugs immediately after a stroke, but many discontinue use over time. Both primary and secondary prevention of stroke are long-term interventions that require patients' acceptance of their condition and collaboration in life-style changes and drug treatments.

This thesis is not about interventions to improve prescribing or patient adherence. We have, however, shown associations between use of drug and different factors that need to be considered when trying to improve the use of drugs. Most interventions that have shown a positive effect on adherence to long-term treatments have been complex and include several different aspects.[124]

Patients should, according to the Swedish Health and Medical Service Act, be included in shaping and carrying out their treatments.[40] A target area of the Swedish national drug strategy is to increase the consensus between patient and prescriber and to increase the patient's understanding of the prescribed

treatments.[41] An external evaluation of Swedish health care published in 2012 concluded that Sweden has made good progress in strengthening legislation on patient involvement but that patients are often not well informed or included in decisions about their own treatment.[125] Focusing on patients' perspectives on disease and treatment is sometimes referred to as patient-centred care. There is no international consensus on a definition of patient-centred care, and other expressions such as relationship-centred, person-centred, and client-centred care are also used.[126] Common themes are included in most of these concepts, including respect for individuality and individual values, social context and relationships, communication, and expert lay knowledge.[126] One description is:

> *"... the ability of the healthcare provider to see the patient as a unique person; to maintain unconditional positive regard; to build effective rapport; to use the bio-psychosocial model; to explore patient beliefs, values and meaning of illness; and to find common ground regarding treatment plans."*[127]

This description highlights the importance of exploring patients' beliefs and meaning of illness and of finding common ground regarding treatments. This thesis does not measure or analyse patient centeredness, but in a sample of stroke patients we have found different perceptions about stroke and different beliefs about medicines. We have also found associations between personal beliefs and adherence to treatment. Patient-centred care has been shown to improve clinical outcome[128-130] and adherence to treatment.[131, 132]

Interventions to improve adherence to treatment need to be developed and tested, but it is unlikely that one single solution will be found that works for all individual patients. Patients need to be treated as individuals not only in diagnosing and choice of medical treatment but also in relation to their own perceptions of their disease and beliefs about treatments. The WHO definition of adherence has been changed to include the word "agree", whether a person's behaviour corresponds with agreed-upon recommendations.[57] However, it is not yet clear if this is just a change in wording or if it reflects an actual change in practice.

Adherence to treatment and individual behaviour in general has proven difficult to influence or change, but if there are reasons behind individual behaviour in using or not using drugs, and non-adherence is not random, it should be possible to find ways to influence behaviour and improve adherence.

Conclusion and future research

Conclusion

In clinical trials, secondary preventive drug treatment after stroke has been shown to be effective in preventing recurrent stroke. A large proportion of Swedish stroke patients were prescribed secondary preventive drugs at discharge from hospital. Most patients initially used the drugs they had been prescribed, but the level of adherence to treatment decreased over time. Preventive treatment is usually considered a long-term intervention. Because of the large number of patients who suffer a stroke the decreasing level of adherence is a public health problem.

Some inequalities were found in use of secondary preventive drugs. Women were prescribed statins and warfarin after ischemic stroke to a lower extent than men. A social stratification in prescribing of statins was also found in which patients with higher income and education were more likely to be prescribed statins at discharge. Patients born outside of Sweden were also more likely to be prescribed statins compared to Swedish-born patients. The differences in prescribing could not be explained by differences in patient characteristics or health and health care-related factors.

Several factors were tested for associations to adherence, and good self-rated health, living in institutions, having used the drug before the stroke, and having a first-ever stroke were associated with adherence. Associations were also found between beliefs about medicines and adherence to treatment. The rather small proportion of patients who self-reported non-adherent behaviour already three months after stroke scored higher on negative statements about medicines and lower on positive statements.

This thesis reflects two aspects of use of drugs after stroke, both how drugs were prescribed and how patients used the drugs that were prescribed for them. The factors tested for association with use of drugs were diverse and were related to demography, disease, health care, socioeconomic status, and patients' personal beliefs. The results in this thesis showed that these factors were associated with use of secondary preventive drugs after stroke. Thus, a broader perspective needs to be used when trying to understand and improve the use of drugs after stroke.

Future research

A significant amount of research has already been carried out into understanding how drugs are used in health care and in society and into understanding what factors influence how drugs are used. The inconsistency in the results from this research is likely related to both the complexity of the research field itself, including human behaviour and interactions between associated factors, and to the inconsistent terminology used in the field of adherence.

Several efforts have been made to suggest a common terminology and definitions to be used in the field of adherence[58-60, 104, 105], but none has so far had a general impact in the field. Although most researchers in the field seem to agree that there are different aspects of drug use to be investigated, a common terminology would improve the possibilitiy to draw conclusions.

Most studies on patient adherence are cross-sectional, but to better understand the reasons for poor patient adherence longitudinal studies are needed. Longitudinal studies to investigate the effect of adherence on treatment outcome, such as stroke recurrence and mortality, are also needed. It is also important that future research focus more on interactions between factors associated with adherence. The many national registers and databases available in Sweden provide for opportunities to include large samples and to follow patients over time. The personal identification number makes it possible to merge different types of variables from different registers and to add variables from registers and databases to data collected for research purposes.

Qualitative studies on non-adherent patients could contribute to the understanding of poor adherence. I believe it is important to include patients' views on the use of drugs to be able to develop an effective intervention to improve the use of drugs. It is also important to include behavioural science, including health psychology, in discussions about use of drugs. Both prescribing of drugs and patient adherence to treatment are acts of human behaviour and as such are influenced by attitudes, emotions, norms, culture, authority, etc. I believe that these aspects must not be forgotten.

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Appendix

Survey questionnaire (in Swedish)

Sjukhuskod:

Patientens personnummer: –

INFORMATION TILL PATIENT OCH/ELLER NÄRSTÅENDE
Angående en vetenskaplig studie om läkemedel 3 månader efter stroke

Information om studien

Läkemedel är en del av behandlingen efter stroke. Vi gör nu en vetenskaplig studie av hur uppfattningar om stroke och läkemedel påverkar hur man tar sina mediciner. Vi inbjuder dig att delta i studien.

Studien genomförs vid Institutionen för folkhälsa och klinisk medicin vid Umeå Universitet. Vi samarbetar med Riks-Stroke som mäter den svenska strokevårdens kvalitet. Även om du väljer att inte delta i studien av läkemedel ber vi att du ändå fyller i enkäten från Riks-Stroke och sänder tillbaka den.

Med mer kunskap om de problem som kan uppstå vid behandling med läkemedel kan vi bättre förstå hur vi minskar risken att på nytt insjukna i stroke. Vi vill därför be dig svara på det medföljande frågeformuläret. När det gått ett år efter ditt insjuknande kommer vi att inbjuda dig att svara på samma frågor. Detta för att kunna följa förändringar över tid.

Om du väljer att delta i denna undersökning kommer dina svar att kompletteras med uppgifter från Riks-Stroke och från Socialstyrelsens Läkemedelsregister med information om receptbelagda läkemedel. Dessutom planerar vi att hämta uppgifter om utbildning, sysselsättning, ursprungsland samt inkomst från Statistiska Centralbyrån. Sedan dessa kompletteringar är gjorda kommer namn och personnummer att omedelbart raderas. Det finns då inte längre någon möjlighet att spåra dig som enskild individ.

Så hanteras dina uppgifter

Riks-Stroke är ett nationellt kvalitetsregister med säte i Västerbottens läns landsting. Syftet är att främja god strokevård för alla, oavsett bostadsort, kön och ålder. Riks-Stroke är skyddat av samma sekretess som råder i övriga delar av sjukvården. Också all information i denna studie kommer att behandlas konfidentiellt. Mer utförlig information om vilka data som registreras i Riks-Stroke och hur dessa data behandlas finns att läsa på det patientinformationsbrev som medföljer detta utskick från Riks-Stroke samt på hemsidan (www.riks-stroke.org).

För denna vetenskapliga studie är Umeå Universitet personuppgiftsansvarig och ansvarar för att data behandlas enligt personuppgiftslagen (PUL). Studien är godkänd av en etikprövningsnämnd.

Deltagande i studien är helt frivilligt och kommer inte på något sätt att påverka den vård du får. Om du valt att svara på enkäten och ångrar dig kan du meddela oss att du inte längre önskar delta. Du har också rätt att begära ut information som är registrerad om dig. Efter komplettering av data från Nationella register och SCB går det dock inte att spåra dig som enskild individ längre.

Det är av stor betydelse att så många som möjligt deltar. Därigenom skapas ett tillförlitligt underlag för att söka förbättringar för de som insjuknat i stroke. Studien kommer att resultera i en vetenskaplig rapport.

Om du inte vill delta i studien ber vi dig att skicka tillbaka enkäten ej fylld. Då slipper du få en påminnelse angående denna studie. Du kan också ringa till den kontaktperson som är ansvarig för registrering i Riks-Stroke (se telefonnummer nedan). Vi ber vi dig fylla i enkäten från Riks-Stroke även om du väljer att inte delta i denna vetenskapliga studie.

Namn.....

Telefon.....

Adress till sjukhus.....

Om du har specifika frågor angående den här vetenskapliga studien om Läkemedel efter stroke ber vi Dig kontakta:

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Enkäten kommer att läsas maskinellt. När du besvarar enkäten ber vi dig därför att tänka på att:

- Använda kulspetspenna med svart eller blå färg, inte röd. Använd inte blyertspenna.
- Markera dina kryss så här: ☒ Inte så här: ☒
- Om du råkar kryssa i fel ruta, stryk över hela rutan och sätt kryss i rätt ruta: ■ ☒

FRÅGOR OM DINA UPPFATTNINGAR OM STROKE

För följande frågor ber vi dig markera det alternativ som bäst överensstämmer med dina uppfattningar:

		Ingen påverkan alls										Påverkar mitt liv i stor utsträckning
		0	1	2	3	4	5	6	7	8	9	10
1.	Hur mycket påverkar din stroke ditt liv?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

		En väldigt kort tid										För evigt
		0	1	2	3	4	5	6	7	8	9	10
2.	Hur länge tror du att du kommer att påverkas av din stroke?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

		Absolut ingen kontroll										Extremt mycket kontroll
		0	1	2	3	4	5	6	7	8	9	10
3.	Hur mycket kontroll känner du att du har över din stroke/dina strokesymtom?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

		Ingen nytta alls										Mycket stor nytta
		0	1	2	3	4	5	6	7	8	9	10
4.	Hur mycket tror du att din nuvarande behandling kan skydda mot ytterligare en stroke?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

		Inga symtom alls										Många allvarliga symtom
		0	1	2	3	4	5	6	7	8	9	10
5.	Hur mycket symtom upplever du av din stroke?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

		Inte orolig alls										Extremt orolig
		0	1	2	3	4	5	6	7	8	9	10
6.	Hur orolig är du för att få ytterligare en stroke?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

		Vet inget alls										Vet väldigt mycket
		0	1	2	3	4	5	6	7	8	9	10
7.	Hur mycket tycker du att du vet om stroke?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

		Påverkas inte alls känslomässigt										Påverkas extremt starkt känslomässigt
		0	1	2	3	4	5	6	7	8	9	10
8.	Hur mycket påverkar din stroke dig känslomässigt? (Blir du till exempel arg, rädd, upprörd eller deprimerad?)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

DINA UPPFATTNINGAR OM LÄKEMEDEL I ALLMÄNNHET

Inga svar är mer rätt eller fel än andra.
Vi är intresserade av Dina personliga uppfattningar.

	Stämmer mycket bra	Stämmer bra	Osäker	Stämmer dåligt	Stämmer inte alls
9. Läkare ordinerar för många läkemedel	☐	☐	☐	☐	☐
10. Människor som använder läkemedel bör göra uppehåll i sin behandling då och då	☐	☐	☐	☐	☐
11. Läkemedel hjälper många människor att leva bättre liv	☐	☐	☐	☐	☐
12. De flesta läkemedel är beroendeframkallande	☐	☐	☐	☐	☐
13. Naturläkemedel är säkrare än traditionella läkemedel	☐	☐	☐	☐	☐
14. Nyttan med läkemedlen uppväger i de flesta fall riskerna	☐	☐	☐	☐	☐
	Stämmer mycket bra	Stämmer bra	Osäker	Stämmer dåligt	Stämmer inte alls
15. Utan läkemedel skulle läkarna ha mindre möjlighet att bota människor	☐	☐	☐	☐	☐
16. Alla läkemedel är gifter	☐	☐	☐	☐	☐
17. Läkemedel gör mer skada än nytta	☐	☐	☐	☐	☐
18. Läkemedel hjälper många människor att leva längre	☐	☐	☐	☐	☐
19. Läkare förlitar sig för mycket på läkemedel	☐	☐	☐	☐	☐
20. Om läkare hade mer tid för sina patienter skulle de ordinera färre läkemedel	☐	☐	☐	☐	☐

DINA UPPFATTNINGAR OM LÄKEMEDEL SOM FÖRSKRIVITS FÖR DIG

Inga svar är mer rätt eller fel än andra.
Vi är intresserade av Dina personliga uppfattningar.

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Uppfattningar om läkemedel som förskrivits för Dig	Stämmer mycket bra	Stämmer bra	Osäker	Stämmer dåligt	Stämmer inte alls
21. Min nuvarande hälsa är beroende av mina läkemedel	☐	☐	☐	☐	☐
22. Det oroar mig att jag måste ta läkemedel	☐	☐	☐	☐	☐
23. Mitt liv skulle vara omöjligt utan mina läkemedel	☐	☐	☐	☐	☐
24. Ibland oroar jag mig för mina läkemedels långsiktiga effekter	☐	☐	☐	☐	☐
25. Utan mina läkemedel skulle jag vara mycket sjuk	☐	☐	☐	☐	☐
	Stämmer mycket bra	**Stämmer bra**	**Osäker**	**Stämmer dåligt**	**Stämmer inte alls**
26. Mina läkemedel är en gåta för mig	☐	☐	☐	☐	☐
27. Min framtida hälsa kommer att bero på mina läkemedel	☐	☐	☐	☐	☐
28. Mina läkemedel stör mitt liv	☐	☐	☐	☐	☐
29. Ibland oroar jag mig över att bli alltför beroende av mina läkemedel	☐	☐	☐	☐	☐
30. Mina läkemedel skyddar mig från att bli sämre	☐	☐	☐	☐	☐

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FRÅGOR OM HUR DU ANVÄNDER DINA MEDICINER

Många människor hittar ett sätt att ta sina mediciner som passar dem. Detta sätt att ta sina mediciner kan skilja sig från det som står på etiketten eller från vad läkaren sagt. Vi skulle vilja ställa några frågor om hur du använder dina mediciner.

Nedan ser du några påståenden som människor har gjort angående hur de använder sina mediciner.

Markera för varje påstående det alternativ som stämmer bäst på dig.

	Alltid	Ofta	Ibland	Sällan	Aldrig
31. Jag glömmer att ta mina mediciner.....	☐	☐	☐	☐	☐
32. Jag ändrar på doseringen av mina mediciner	☐	☐	☐	☐	☐
33. Jag gör uppehåll i min medicinering	☐	☐	☐	☐	☐
34. Jag bestämmer mig för att hoppa över en dos	☐	☐	☐	☐	☐
35. Jag tar mindre än jag har blivit ordinerad.....	☐	☐	☐	☐	☐