Outcome of Stroke Prevention

Analyses Based on Data from Riks-Stroke and Other Swedish National Registers

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Abstract

The aim of this thesis was to explore variations in stroke prevention and the effect of prevention on outcome. The studies were based on patients registered in the Swedish Stroke Register between 2001 and 2009 and although used to different extents in each paper, additional information was retrieved through linkage to The National Patient Register, the Cause of Death Register, the Prescribed Drug Register and the Total Population Register.

Cardiovascular risk factors were prevalent among ischemic stroke (IS) patients; however, they were not always prescribed the drugs recommended, and increasing age was an important negative predictor (Paper I).

After IS, the rate of hemorrhage in patients prescribed antiplatelet agents (2.4 per 100 person-years) was double to results from randomized controlled trails, but was similar for patients prescribed warfarin (2.5 per 100 person-years). Age ≥75 years and previous hemorrhage were associated with a moderately increased risk of future hemorrhage (Paper II).

Among IS patients with atrial fibrillation, one-third was prescribed warfarin and two-thirds were prescribed antiplatelets. After adjustment for a propensity score (used to adjust for the non-randomized design), warfarin was associated with a reduced risk of death (0.67; 95% CI, 0.63-0.71) (Paper III). The rate of subsequent hemorrhagic stroke was 0.4 per 100 person-years and the risk did not change (HR 1.04; 95% CI, 0.73-1.48) when later years of the 2000s (inclusion period 2005-8: follow-up until 2009) was compared with earlier years (inclusion period 2001-4: follow-up until 2005) (Paper IV, cohort).

Although the risk of first-ever hemorrhagic stroke more than doubled with warfarin than without, the risk did not change between 2006 and 2009 (Paper IV, case-control).

In summary, the prescription of secondary preventive drugs varies with age, even though cardiovascular risk factors are prevalent in all ages. The risk of death and hemorrhage are affected by the type of antithrombotic prescribed. Therefore, it is important individual’s stroke and bleeding risks in stroke prevention are assessed.

Keywords: Stroke, Epidemiology, Age groups, Risk factors, Atrial fibrillation, Secondary prevention, Anticoagulants, Antiplatelets, Hemorrhage, Mortality.

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To Oskar
List of Papers

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


III Åsberg S, Eriksson M, Henriksson KM, Terént A. Reduced risk of death with warfarin: Results of an observational nationwide study of 20 442 patients with ischemic stroke and atrial fibrillation. Accepted Jan 24, 2012 for publication in Int J Stroke.

IV Åsberg S, Eriksson M, Henriksson KM, Terént A. The risk of warfarin-associated hemorrhagic stroke for the years 2001 to 2009: An analysis based on 20 486 stroke patients in the Swedish Stroke Register. Submitted manuscript

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Abbreviations

AC Anticoagulants
ACE Angiotensin-converting enzyme
ADL Activities of daily living
AP Antiplatelets
AF Atrial fibrillation
AT Antithrombotics (anticoagulants and antiplatelets)
ATC Anatomical therapeutic chemical
CDR Cause of Death Register
CI Confidence interval
CHF Congestive heart failure
CT Computer tomography
DM Diabetes mellitus
GI Gastrointestinal
HR Hazard ratio
HS Hemorrhagic stroke
HT Hypertension
IC Intracranial
ICD International classification of diseases
ICH Intracerebral hemorrhage
INR International normalized ratio
IS Ischemic stroke
mRS Modified Rankin scale
NPR National Patient Register
NSAID Non-steroidal anti-inflammatory drug
OR Odds ratio
RCT Randomized controlled trials
SD Standard deviation
SEK Swedish currency
TIA Transient ischemic attack
TPR Total Population Register
WHO World Health Organization
Introduction

Stroke is one of the most widespread manifestations of vascular disease. In Sweden, approximately 30,000 people suffer strokes every year,\(^1\) of which 23,000 have a first event of stroke (first-ever stroke).\(^2\) The number of stroke victims is expected to rise as the percentage of senior citizens in the country increases.\(^3\) Stroke is the most common cause of neurological disability among adults in industrialized countries,\(^4\) and reducing stroke burden, through prevention and care for first and recurrent events, is a major task for health care systems. The management of stroke includes interventions before (primary) and after (secondary) stroke, and interventions in the acute phase and in the long term thereafter (Figure 1).

Figure 1. Approaches for management of stroke.

This thesis focuses on the pharmacological prevention of stroke, particularly secondary prevention. Although several randomized controlled trials (RCT) evaluated the benefits and risks of drugs used for the prevention of stroke,\(^5\)-\(^8\) the patients included in the trials do not always reflect the patients seen in clinical practice, and particularly elderly and fragile patients are excluded. In contrast to in RCT, in observational studies (such as Papers I-IV), which subjects are exposed to a new treatment cannot be determined. Hence, observational studies can only observe an association between exposure and outcome, and cannot imply a causal relationship.

However, as some groups of patients (such as the elderly) are difficult to allocate randomly to exposure and as most groups are difficult to follow over a long-time, observational studies are a vital tool for describing the world outside of RCT.
Stroke and stroke subtypes

The World Health Organization (WHO) defines stroke as:

“rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, with symptoms, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin.”


A stroke is caused by the interruption of blood supply to the brain, from either lack of blood flow (ischemia) or leakage of blood (hemorrhage). This disruption to the supply of oxygen and nutrients causes damage to the brain tissue. In a transient ischemic attack (TIA), the interruption of blood supply to the brain is temporary, and by definition, the symptoms last less than 24 hours. The most common symptom of a stroke, or TIA, is sudden weakness or numbness to the face, arm or leg, most often on one side of the body. The effects of a stroke depend on which part of the brain is injured and how severely it is affected. As the management of ischemic and hemorrhagic stroke is different, the distinction between these subtypes is important for acute management.

Ischemic stroke causes approximately 85% of all stroke cases in high-income countries, and is usually arterial (large or small vessels) or cardioembolic in origin. The WHO definition of hemorrhagic stroke comprises subarachnoid hemorrhage, and other definitions include tumor or trauma-related hemorrhages, in addition to primary intracerebral hemorrhage (ICH). In the main source for this thesis (The Swedish Stroke Register), patients with ischemic stroke, primary ICH (herein referred to as hemorrhagic stroke) and stroke not specified as ischemic or hemorrhagic are eligible for registration.

Risk factors for stroke

Certain individual and population characteristics (risk factors) are associated with stroke. The impact of a risk factor is considered low, if the proportion of stroke cases attributed to the risk factor is low. However, a strong risk factor associated with a modest increase may be important for stroke incidence if the risk factor is prevalent or the background risk of stroke in the population is high.

Many risk factors for stroke are the same as for other consequences of large vessel atherosclerosis (such as myocardial infarction), the majority of strokes are ischemic and most ischemic strokes are caused by large vessel disease. Even so, stroke has other pathologies than large artery
atherosclerosis, and depending on the origin of the stroke, the risk factors could differ to those for myocardial infarction.\textsuperscript{12}

The risk factors for stroke are essentially the same for both men and women,\textsuperscript{13} even if some risk factors, e.g. atrial fibrillation (AF), increase the risk of developing stroke among women.\textsuperscript{14} In both sexes, increasing age is a strong risk factor for both ischemic and hemorrhagic strokes, with half of all strokes occurring in people $\geq 75$ years (Figure 2).\textsuperscript{15} As the risk of stroke increases with age and women tend to live longer than men, more women have strokes each year than men do.\textsuperscript{16}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Age-specific incidence of ischemic stroke and intracerebral hemorrhage in men and women in a vascular study population.\textsuperscript{17}}
\end{figure}

In addition to age, there are five important modifiable risk factors for ischemic stroke: these are hypertension, diabetes mellitus, smoking, AF and physical inactivity.\textsuperscript{15, 18} Hypertension is the most important modifiable risk factor for hemorrhagic stroke,\textsuperscript{19} although other, often interrelated, factors can contribute towards developing hemorrhagic stroke, including structural factors, e.g. vascular malformations, and factors affecting hemostasis, e.g. antithrombotic therapy. Further associated factors, reported from observational studies are diabetes mellitus, smoking and high alcohol intake.\textsuperscript{19, 20}

Hypertension is defined as blood pressure $\geq 140/90$ mmHg,\textsuperscript{21} and accounts for approximately 40% of all strokes and is a more potent risk factor for hemorrhagic stroke than for ischemic stroke.\textsuperscript{12} Due to its high prevalence, hypertension is the main modifiable risk factor for stroke; by comparison, AF is estimated to be responsible for approximately 20% of all ischemic strokes.\textsuperscript{22} Thus, hypertension is responsible for a greater proportion of the global burden of stroke than AF, although the risk of having a stroke is higher in an individual with AF than in an individual with hypertension.
Furthermore, ischemic stroke in association with AF is often fatal, and patients who survive are more disabled and likely to suffer a recurrence than patients with other causes of stroke are.\textsuperscript{23, 24}

Atrial fibrillation and predictive scores

The prevalence of AF increases with age in both sexes and is higher in older women (Figure 3).\textsuperscript{22} The absolute risk of stroke varies substantially among AF patients and depends on age and the presence of other stroke risk factors. The estimation of an individual’s stroke risk is crucial when prescribing antithrombotic stroke prophylaxis.

Figure 3. In-hospital patients with atrial fibrillation, per 100 000 Swedish inhabitants in 2010. Data from the public database of the National Board of Health and Welfare.\textsuperscript{25}

All patients with previous ischemic stroke, or TIA, have a high risk of recurrent stroke, therefore, these patients should be treated with anticoagulants and it becomes unnecessary for any further stratification by risk. Nevertheless, risk stratification schemes are valuable in primary prevention and if anticoagulant therapy is questioned. The most validated and widespread stratification scheme is the CHADS\textsubscript{2} index.\textsuperscript{26} In this index, congestive heart failure, hypertension, age $\geq$75 years and diabetes mellitus are awarded 1 point each (1p) and previous stroke or TIA are awarded 2 points (2p).

In primary prevention, the CHADS\textsubscript{2} index can be extended to the CHA\textsubscript{2}DS\textsubscript{2}-VASc for enabling precise risk stratification of AF patients with low risk (i.e. CHADS\textsubscript{2} score of $<$2p).\textsuperscript{27} The extended CHA\textsubscript{2}DS\textsubscript{2}-VASc scheme is used in Swedish and European guidelines,\textsuperscript{27, 28} and considers additional stroke risk factors, such as age 65–74 years, vascular disease
(e.g. myocardial infarction and peripheral artery disease) and female sex (Table 1).

Table 1. Risk stratification according to the CHADS2 and the CHA2DS2-VASc index

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>C Congestive heart failure/LV dysfunction</td>
<td>1</td>
</tr>
<tr>
<td>H Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A Age ≥75 yrs</td>
<td>2</td>
</tr>
<tr>
<td>D Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>S Stroke or TIA</td>
<td>2</td>
</tr>
<tr>
<td>V Vascular disease</td>
<td>1</td>
</tr>
<tr>
<td>A Age 65-74</td>
<td>1</td>
</tr>
<tr>
<td>S Sex category (i.e. female)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Maximum score</strong></td>
<td><strong>9</strong></td>
</tr>
</tbody>
</table>

Bold letters indicate the original CHADS2 index, LV=left ventricular, TIA=transient ischemic attack.

In AF patients with CHADS2 score ≥2, anticoagulation therapy is recommended, if not contraindicated, and should be considered in patients with CHA2DS2-VASc score of 1. However, anticoagulation therapy is not recommended for CHA2DS2-VASc scores of 0 or in the presence of contraindications: in these cases, antiplatelet agents or no antithrombotic therapy is recommended.

Anticoagulants, such as warfarin, are associated with an increased risk of bleeding, and hemorrhagic stroke is the most feared complication. In RCT of secondary prevention after stroke, the risk of severe hemorrhage varies between 2% and 5% per year in patients randomized to warfarin, whereas, the risk is lower, (1-2% per year) in patients randomized to antiplatelet agents.

However, a meta-analysis of 5 RCT on primary prevention, which included patients with AF and other indications for warfarin, failed to demonstrate a significant difference between aspirin and warfarin in the risk of major bleeding.

In observational studies, the risk of hemorrhage varies even more: 2-8% among patients who use warfarin and 0-4% among patients who use antiplatelets. High age and previous hemorrhages are included as risk factors in a recently proposed score for the risk of hemorrhage: HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio (INR), Elderly, Drugs/alcohol concomitantly). Therefore, the assessment of an individual’s stroke and bleeding risk is crucial when prescribing antithrombotic stroke prophylaxis.
Prevention of stroke

The most effective approach for treating stroke is prevention; the reduced mortality from stroke during the 2000s is largely attributable to the improved control of risk factors. Although primary stroke prevention is important for reducing the burden of stroke, effective secondary prevention is also essential, especially as individuals with prior stroke are at greater risk of developing stroke than individuals without a history of stroke. Secondary prevention in the acute setting involves the regulation of blood pressure and glucose levels, surgery (carotid endarterectomy, clipping or coiling of aneurysms), and antithrombotic therapy for ischemic stroke.

Long-term secondary prevention

This thesis focuses on outcome associated with long-term pharmaceutical prevention of recurrent stroke, particularly the prescription of antithrombotic therapy (antiplatelets and warfarin) and the prescription of angiotensin-converting enzymes (ACE) inhibitors, and statins.

Antiplatelet agents

In the case of ischemic stroke of presumed arterial (large or small vessels) origin, antiplatelets are recommended for the stroke prevention, but not anticoagulants, such as warfarin. Antiplatelet drugs include aspirin, aspirin in combination with dipyridamole, and clopidogrel; and these drugs reduce the relative risk of vascular events (including stroke) by 22%. Although the differences among the agents are small, these differences might still be important for therapeutic selection and guidelines about which of the drugs should be recommend as first-line treatment vary.

Aspirin, the most studied agent, reduces the risk of recurrent stroke by 15-18% and the risk of any vascular event by 22%. Although aspirin is the least expensive antiplatelet drug in Sweden (0.60 SEK per day in 2012), it increases the risk of bleeding, especially in the gastrointestinal tract and in older patients.

The combination of aspirin with dipyridamole (5.60 SEK per day) prevents 1 vascular event per 100 patients treated per year, compared to aspirin alone, but is not as well tolerated due to headaches.

There is a similar risk reduction (to the combination of aspirin with dipyridamole) in vascular events with clopidogrel (1.50 SEK per day), but not to a significant level in patients with previous ischemic stroke.

Anticoagulant agents

In the case of ischemic stroke of cardiac origin (most commonly AF), anticoagulants are recommended if there are no contraindications. In several RCT, warfarin is demonstrated to be superior in efficacy over
antiplatelet therapy. An adjusted-dose warfarin (INR 2.0-3.0) can reduce the risk of stroke by 40% compared to antiplatelet agents, and by 60% compared to placebo (no antithrombotic drugs), and this proportional risk reduction is consistent even in patients ≥75 years. However, only two-thirds of eligible patients are prescribed warfarin: this suboptimal use may relate to a poor appreciation of the risk-benefit ratio, with both the risks of warfarin therapy and the benefits of antiplatelet agents being overestimated. Nevertheless, the dispensing of warfarin to Swedish inhabitants aged 65-74 years has increased by >10% (3.7% in 2006 to 4.3% in 2009), this could reflect both an increase in prevalence or detection of AF, and a change in the characteristics of patients considered eligible for anticoagulation therapy. The implication of this changing medical landscape on the risk-benefit ratio of warfarin is unknown.

The effect of warfarin (i.e. INR) is monitored through blood tests, and warfarin therapy has major limitations. Warfarin has multiple drug and dietary interactions and genetic variability in the dose-response effect, which complicates the INR control. A major complication of anticoagulant therapy is hemorrhage, and the risk increases if the patient is over-anticoagulated (i.e. INR>3.0 in warfarin therapy). Conversely, the risk of ischemic stroke and the severity of stroke increases if INR is <2.0, which emphasizes the importance of controlling INR. Swedish patients treated with warfarin are generally well monitored, with a mean time in therapeutic range (INR 2-3) of 75%.

In the 2011 Swedish guidelines, dabigatran, a new anticoagulant that does not need monitoring, is recommended as a second-line drug for stroke prevention in AF patients, and other anticoagulant agents, such as apixaban and rivaroxaban are emerging. However, for patients with >70% time in therapeutic INR range, the cost-effectiveness of dabigatran is questioned. The annual cost per patient of dabigatran is estimated as 10 900 SEK and of warfarin as 5700 SEK, including INR control.

**Antihypertensive agents**

There are direct and continuous relations of both diastolic pressure and systolic pressure with stroke, without a clear lower threshold. For every 10 mmHg reduction in systolic blood pressure, the relative risk of stroke decreases by about one-third. Although life-style modifications can achieve a reduction in blood pressure of 5 mmHg, pharmaceutical therapy with antihypertensive agents, such as diuretics, angiotensin-converting enzyme (ACE) inhibitors, beta-receptor blockers, calcium-channel blockers and angiotensin-receptor blockers, is often required.

There is a lack of direct comparisons of these agents in patients with a history of stroke. Besides not recommending beta-receptor blockers, current guidelines focus more on the importance of treatment than on choice of spe-
cific agent, although in previous guidelines, ACE inhibitors had higher priority than the other agents.

Lipid-lowering agents
The association between lipid concentrations and risk is weaker for ischemic stroke than for myocardial infarction; statins are reported to reduce the risk of stroke in patients with ischemic heart disease, but not in those with a history of stroke. However, a secondary stroke prevention trial of statins, which included patients up to the age of 92 years, identified a reduced risk of stroke even in patients with a history of stroke. Statin agents are recommended for ischemic stroke patients with normal or elevated blood lipids, but not to hemorrhagic stroke patients, as there may be an increased risk of future hemorrhagic stroke.
Aims

The overall aim of this thesis was to explore variations in stroke prevention and its effect on outcome, reflected by Riks-Stroke, the Swedish Stroke Register.

The specific aims were:

**Paper I:** to investigate the prescription of secondary prevention in patients with first-ever ischemic stroke in relation to age and risk of death.

**Paper II:** to investigate the risk of major hemorrhage after first-ever ischemic stroke in relation to age and antithrombotic therapy.

**Paper III:** to investigate the potential effect of warfarin on long-term mortality in patients with first-ever ischemic stroke and atrial fibrillation.

**Paper IV:** to investigate time-variations in the risk of warfarin-associated hemorrhagic stroke, in patients with first-ever hemorrhagic stroke compared to stroke-free controls and in patients with a previous ischemic stroke.
Methods

National register in Sweden

Sweden has a long tradition of keeping local records on the population. In the late 1600s, the first nationwide report system held by the Swedish state church was first introduced and served to keep a national census and enroll soldiers into the army. In 1744, the first Swedish scientific research paper in vital statistics was published by Pehr Elvius (List of the number of children born annually in the city of U... over the last 50 years. Along with comments on the above). Today, the National Tax Board is responsible for both the national civil registration and the assignment of a unique personal identification number (PIN) to each individual resident in Sweden. The PIN is the foundation of Swedish register-based studies.

Classification systems

In addition to PIN, other key stones in register-based studies are standardized classification of diseases and drugs. These classifications provide the basis for the compilation of national mortality and morbidity statistics, and enable the storage and retrieval of information for clinical, epidemiological and quality purposes.

The International Classification of Diseases (ICD) is used to classify diseases and other health problems into an alphanumeric code. Since 1997, the current version of ICD, the 10th revision, has been used in Sweden. Although automatic conversion between previous revisions and ICD-10 is not possible, the World Health Organization has published translator tables that enable manual bridging from ICD-9 into ICD-10. These translator tables were used in the studies for Papers I-IV when codes of (previous) stroke, comorbid disease and hemorrhage were identified.

In the Anatomical Therapeutic Chemical (ATC) classification system, drugs (i.e. the active substances) are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties.

Although used to different extents in each paper of this thesis, five registers were linked through the patients’ unique PIN. The Swedish Stroke Register (Riks-Stroke) was used to identify the index stroke hospitalization, and provided demographic and medical data. The National Patient Register pro-
vided additional medical data. The Swedish Cause of Death Register provided the dates and causes of death. The Prescribed Drug Register provided data on dispensed study drugs and the Total Population Register was the source for stroke-free controls in Paper IV, see flow-chart in Figure 4.

![Flow-chart of patients included in Paper I-IV and national registers used. The dotted lines indicate sub-groups, c-c=case-control.](image)

The Swedish Stroke Register (*Riks-Stroke*)

A system of national quality registries is established in the Swedish health and medical services and approximately 100 registries receive central funding. Of these, nine registers are classed as high quality registers and receive funding on a yearly basis, including *Riks-Stroke*, the national quality register for stroke care, which was initiated in 1994. National quality registries contain individualized data within healthcare production concerning patient problems, medical interventions, and outcomes after treatment. Since 1998, *Riks-Stroke*, has included all hospitals, admitting patients with acute stroke, and covers more than 80% of all stroke events in Sweden. A case-by-case validation of *Riks-Stroke* indicates patients who die early, who are not treated at a stroke unit, or who are cared for in a nursing home are less likely to be included in the register. *Riks-Stroke* contains data on age, sex, cardiovascular risk factors, drug therapy, and dependency in activities of daily living (ADL). Cardiovascular risk factors comprise diabetes mellitus, AF, hypertension and smoking history. Until 2004, *Riks-Stroke* only registered antithrombotic drugs, but thereafter, included other cardiovascular preventive drugs (e.g. statins, antihypertensive agents).
The National Patient Register

Information on hospitalization before and after the index stroke was obtained from the National Patient Register (NPR), which had complete national coverage since 1987 and was previously known as the Swedish Hospital Discharge Register. The NPR contains data on main and secondary diagnoses for each hospitalization; it is updated annually. The overall predictive value of diagnosis in the register is estimated as 85–95%. In this thesis, the NPR was searched for diagnosis registered in 1987 and later. Diagnoses in the NPR were coded according to the ICD 9th revision up until 1997, thereafter the 10th revision (Table 2).

Table 2. Codes of diagnosis used in Papers I-IV from ICD, 9th and 10th revisions

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>ICD-9</th>
<th>ICD-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic stroke</td>
<td>431</td>
<td>I61</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>433</td>
<td>I63</td>
</tr>
<tr>
<td>Unspecified stroke</td>
<td>434</td>
<td>I64</td>
</tr>
<tr>
<td>TIA</td>
<td>435</td>
<td>G45</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>427.3</td>
<td>I48</td>
</tr>
<tr>
<td>Heart failure</td>
<td>428-429</td>
<td>I50</td>
</tr>
<tr>
<td>Hypertension</td>
<td>401-405</td>
<td>I10-15</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>250</td>
<td>E10-14</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>410-414</td>
<td>I20-25</td>
</tr>
<tr>
<td>Heart valve disease</td>
<td>394-397, 424, 746</td>
<td>I05-08, I34-39, Q22-23</td>
</tr>
<tr>
<td>Cancer</td>
<td>140-208</td>
<td>C00-97</td>
</tr>
<tr>
<td>Mental/behavioral disorder</td>
<td>290-319</td>
<td>F00-99</td>
</tr>
</tbody>
</table>

ICD=International classification of diseases, TIA=transient ischemic attack

The Cause of Death Register

The Swedish Cause of Death Register comprises all deaths among Swedish residents, whether the death occurred in Sweden or not. Even though there is no loss of individuals, the accuracy of the underlying cause of death is only estimated to be correct for 77% of deaths: the precision is higher for cancer (90%) and ischemic heart disease (87%), but lower for cerebrovascular disease (68%) and other heart disease (65%). However, the diagnostic groups remain stable even after correction for the underlying cause of death, as gains and losses after correction often cancel out each other.

The Prescribed Drug Register

The Prescribed Drug Register started in July 2005 and provides complete national data on all dispensed prescriptions to the whole Swedish population, and all drugs are classified according to the ATC classification system. This register was only used in Paper IV (case-control), where utilization
was defined as $\geq 1$ expenditures of the study drugs during a 6-month period before the index (hemorrhagic) stroke.

The Total Population Register

The Total Population Register (TPR) is maintained by Statistics Sweden and is the basis for all official population statistics and includes names, personal identity numbers, place of birth, civil status, spouse, children, parents, address, and immigration data. Since 1969, the TPR has been the base register for the official Population Statistics and is updated daily with data on population changes from the Tax Authorities.

Outcome assessments

Throughout the thesis, the effect of secondary preventive drugs on the outcome after stroke was estimated. As a register-based study, the outcome measurement was based on available information and definitions.

The different outcomes in Papers I-IV were:
1. Death
   a. from any cause
   b. from specified cause
2. Hemorrhage
   a. major
   b. fatal
3. Stroke recurrence

All-cause mortality is based on the date of death and is unambiguous. However, cause of death is based on death certificates; this reflects the quality and thoroughness of the examination on the cause of death and the accuracy of the physician reporting the findings on the death certificate. There is a delay in the cause of death statistics. For the cohort of patients with stroke in 2001-2005, dates of death were available until February 7, 2007, but causes of deaths were only available until December 31, 2004.

As there was no access to patients’ chart or medical history, other than through registers, the ICD was searched for possible bleeding diagnosis that included bleeding, hematoma or blood. Hematologic diseases, traumatic diseases (unless intracranial) and bleeding diagnosis related to pregnancy and delivery were excluded.

Initially, only the first three characters in the ICD-10 code were used, which is accurate when defining e.g. hemorrhagic stroke (I61) but inaccurate when defining e.g. epidural hemorrhage (S06.4) as concussion (S06.0) also
is included. Hence, the fourth ICD character in the definition of hemorrhages was included, which rendered half as many events as the initial search.

There are numerous options for defining a major hemorrhage, including hospitalization, the need for blood transfusions, a reduction in hemoglobin concentration by $\geq 20$ g/L, and the involvement of a critical site,\textsuperscript{84-86} and what makes a major hemorrhage fatal, such as noted in death certificate or if death occur within a certain period.\textsuperscript{87, 88} In this thesis, major hemorrhage was defined as an admission to a Swedish hospital with a hemorrhage diagnosis, which was classified as fatal if death occurred within 30 days of the event: for intracranial hemorrhages (critical site), both the main and secondary diagnoses were included, but only main diagnoses of hemorrhages that occurred in other locations. In the period before and after the index stroke, only the first hemorrhage was considered, withholding recurrent events. The codes for the hemorrhage diagnosis used are presented in Table 3 (also Supplemental Table in Paper II), and fatal hemorrhages were identified through the time (30d) to death (Paper II). However, in the study for Paper III, death certificates were examined to identify causes of death rather than defining the lethality of a specified event.

As late effects of stroke (ICD-10: I69) sometimes are incorrectly registered as acute stroke (ICD-10: I61, I63) in the NPR,\textsuperscript{77} it was an unsatisfactory source for stroke recurrence. Thus Riks-Stroke was used as the source for recurrent events of stroke (Paper IV, cohort). However, one shortcoming with this approach was that Riks-Stroke only registers preceding events after a washout period of one month, and thus, excludes the early high-risk period.
### Table 3. Codes of hemorrhage diagnosis from ICD, 9th and 10th revisions

<table>
<thead>
<tr>
<th>Location</th>
<th>ICD-9</th>
<th>ICD-10</th>
<th>Type of Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial</td>
<td>430, 431, 432</td>
<td>I60, I61, I62</td>
<td>Subarachnoid hemorrhage, Intracerebral hemorrhage, Other non-traumatic intracranial hemorrhage</td>
</tr>
<tr>
<td></td>
<td>852</td>
<td>S06.4-6</td>
<td>Epidural hemorrhage, traumatic subdural and subarachnoid hemorrhages</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>455C, F, W</td>
<td>I84.1,4,8</td>
<td>Hemorrhoids with bleeding</td>
</tr>
<tr>
<td></td>
<td>456A</td>
<td>I85.0</td>
<td>Esophageal varices with bleeding</td>
</tr>
<tr>
<td></td>
<td>530H</td>
<td>K22.6</td>
<td>Gastro-esophageal laceration-hemorrhage syndrome</td>
</tr>
<tr>
<td></td>
<td>531-534</td>
<td>K25-28</td>
<td>Peptic ulcer disease</td>
</tr>
<tr>
<td></td>
<td>535, 578</td>
<td>K29.0</td>
<td>Acute hemorrhagic gastritis</td>
</tr>
<tr>
<td></td>
<td>569D</td>
<td>K62.5</td>
<td>Hemorrhage of anus and rectum</td>
</tr>
<tr>
<td></td>
<td>578A</td>
<td>K92.0</td>
<td>Hematemesis</td>
</tr>
<tr>
<td></td>
<td>578B</td>
<td>K92.1</td>
<td>Melena</td>
</tr>
<tr>
<td></td>
<td>578X</td>
<td>K92.2</td>
<td>Gastrointestinal hemorrhage, unspecified</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye</td>
<td>372H</td>
<td>H11.3</td>
<td>Conjunctival hemorrhage</td>
</tr>
<tr>
<td></td>
<td>363G</td>
<td>H31.3</td>
<td>Choroidal hemorrhage</td>
</tr>
<tr>
<td></td>
<td>362W</td>
<td>H35.6</td>
<td>Retinal hemorrhage</td>
</tr>
<tr>
<td></td>
<td>379C</td>
<td>H43.1</td>
<td>Vitreous hemorrhage</td>
</tr>
<tr>
<td>Joint</td>
<td>719B</td>
<td>M25.0</td>
<td>Hemarthrosis</td>
</tr>
<tr>
<td>Urogenital</td>
<td>599H</td>
<td>R31</td>
<td>Unspecified hematuria</td>
</tr>
<tr>
<td></td>
<td>602B</td>
<td>N42.1</td>
<td>Congestion and hemorrhage of prostate</td>
</tr>
<tr>
<td></td>
<td>626W, X</td>
<td>N93.8-9</td>
<td>Abnormal uterine and vaginal bleeding</td>
</tr>
<tr>
<td></td>
<td>627A, B</td>
<td>N95.0</td>
<td>Postmenopausal bleeding</td>
</tr>
<tr>
<td>Nose &amp; throat</td>
<td>784H</td>
<td>R04.0</td>
<td>Epistaxis</td>
</tr>
<tr>
<td></td>
<td>784W</td>
<td>R04.1</td>
<td>Hemorrhage from throat</td>
</tr>
<tr>
<td></td>
<td>786D</td>
<td>R04.2</td>
<td>Hemoptysis</td>
</tr>
<tr>
<td></td>
<td>784W</td>
<td>R04.8</td>
<td>Hemorrhage from other sites in respiratory passages</td>
</tr>
<tr>
<td></td>
<td>786D</td>
<td>R04.9</td>
<td>Hemorrhage from respiratory passages, unspecified</td>
</tr>
<tr>
<td>NOS</td>
<td>459A</td>
<td>R58.9</td>
<td>Hemorrhage, not elsewhere classified</td>
</tr>
</tbody>
</table>

ICD=International classification of diseases

### Statistical methods

The statistical analyses were both descriptive (means, proportions, rates) and analytical (univariable and multivariable models). Different patient strata were compared by $\chi^2$-tests for categorical variables and $t$-test or (when not-normally distributed) Wilcoxon Mann-Whitney $U$-test for continuous variables. Before explanatory variables (e.g. confounders) were included in the multivariable regression models, unadjusted (i.e. crude or univariable) analyses were conducted.
Analyzes were performed to estimate:

1. odds ratios (OR) for
   a. prescription of drugs or concomitant disease (Papers I & III-IV);
   b. the risk for warfarin-associated hemorrhagic stroke (Paper IV)

2. hazard ratio (HR) for
   a. death in patients with secondary prevention and those without secondary prevention (Papers I & III);
   b. hemorrhage rate (Paper II)
      i. in patients ≥75 years and younger patients;
      ii. in patients with previous bleedings and those lacking a history of bleeding;

Although used differently use in among the studies, the explanatory variables were age, sex, comorbid diseases, drug therapies, ADL function, index year, and discharge hospital. Logistic regression models were used to predict binary outcomes in the presence of one or several explanatory variables and to estimate a propensity score which expressed the likelihood of the outcome given the presence of the explanatory variables.\textsuperscript{89, 90} Conditional logistic regression was used to predict the outcome for cases relative to controls in Paper IV (case-control).

When time to outcome was the focus, Cox proportional hazard regression models were used. The underlying assumption of this model is proportional hazard, i.e. the ratio between the exposed and unexposed individuals remains constant at any time the ratio is considered. To detect any major deviations from this assumption, Kaplan-Meier curves were examined.

Subgroup analyses were used to estimate the association of exposure and outcome in a subset of patients, such as by functional status or age. Sensitivity analyses determined how robust the results were to changes in how the study was done. SPSS (IBM SPSS Statistics) version 15.01.1, 18.0 and 20.0 were used for the analyses and the level for significance was set to 0.05.

Ethical considerations

All analyses were performed in agreement with the privacy legislation in Sweden. The studies for Papers I-III were approved by the Ethical Review Board at Umeå University, Sweden in May 5, 2006 (Reg. No. 69106), and the study for Paper IV by the Ethical Review Board at Uppsala University, Sweden in December 2, 2009 (Reg. No. 2009/355).
Results

Age and secondary prevention after ischemic stroke (Paper I)

Patients (n=14,529) with a first-ever, non-fatal ischemic stroke and discharged alive in 2005 were included in Paper I (Figure 4). As Riks-Stroke began registering cardiovascular preventive drugs in 2004, other than antithrombotic drugs, 2005 was chosen as inclusion period.

The proportion of patients’ prescribed secondary preventive drugs at discharge differed by age and type of drug (Table 2 in Paper I). In addition to unadjusted frequencies, the odds for prescription of secondary preventive drugs were examined. With increasing age, the adjusted OR for antiplatelet prescription increased moderately, whereas the corresponding OR for ACE-inhibitor, statin, and warfarin decreased substantially (Table 3 in Paper I). The prescription of antiplatelet drugs at discharge was dominated by aspirin (90%), followed by dipyridamole (5%) and clopidogrel (5%).

Three months after stroke, the patients were contacted by the stroke unit where they were treated and asked to answer a questionnaire. The answers, registered in Riks-Stroke, covering the patients’ living arrangement, ADL activity and need for support, were transformed into an estimated grade on the modified Rankin Scale (mRS).91 The mRS, graded from zero to five, is a frequently used tool to evaluate recovery and functional impairment after stroke.92 A higher grade indicates a more severe stroke.

From 3,741 individuals with missing data on the variables in the questionnaire, 27% died within 90 days and 73% were either lost to follow-up or had incomplete answers. To minimize bias derived from selection, the characteristics of the patients without complete 3-month follow-up were compared to the original cohort (Table 4). The patients who died before follow-up were older and had more cardiovascular risk factors and those with no or incomplete follow-up had higher case fatality but a similar risk profile to patients with complete follow-up. Despite these differences, the selection of 10,788 patients was considered a representative sample from the original cohort of 14,529.
Table 4. Description of patients lost to the 3-month follow-up

<table>
<thead>
<tr>
<th>Death before follow-up (n=1010)</th>
<th>No/incomplete follow-up (n=2731)</th>
<th>Complete follow-up (n=10 788)</th>
<th>Original cohort (n=14 529)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean total follow-up (days)</td>
<td>44</td>
<td>518</td>
<td>557</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>83.0</td>
<td>75.0</td>
<td>74.2</td>
</tr>
<tr>
<td>Fatality during study period</td>
<td>100.0</td>
<td>21.5</td>
<td>10.7</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20.0</td>
<td>19.2</td>
<td>18.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>53.4</td>
<td>49.0</td>
<td>52.3</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>40.2</td>
<td>27.1</td>
<td>24.2</td>
</tr>
<tr>
<td>No study risk factor</td>
<td>21.2</td>
<td>25.3</td>
<td>26.8</td>
</tr>
</tbody>
</table>

All values are percentages except for days of total follow-up and age.

HR for death in association with secondary preventive drugs were estimated in 10 788 patients who were alive and had complete follow-up 3 months after the index stroke. After adjustment, the HR for death was lower among patients’ prescribed statin or warfarin (Figure 5).

![Figure 5](image-url)

Figure 5. Survival function for the prescription of statins to 10 788 patients and for the prescription of anticoagulants (warfarin) to 2607 patients with atrial fibrillation.

In a subgroup analysis, the stratum specific HR for death by age and functional status (Table 5) were approximately the same as in the original analyzes for all therapies, with the exception of increased HR estimate of death related to antiplatelets in younger patients with no or minor functional impairment. The association between antithrombotic therapies and risk for death was further analyzed in Paper III.
Table 5. Original and stratum specific adjusted hazard ratios for death

<table>
<thead>
<tr>
<th></th>
<th>Adjusted HR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Original model</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>0.83 (0.68-1.01)</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>1.00 (0.87-1.14)</td>
</tr>
<tr>
<td>Statins</td>
<td>0.78 (0.67-0.91)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>0.58 (0.44-0.76)</td>
</tr>
</tbody>
</table>

HR=hazard ratio, mRS=modified Rankin scale. All estimates are adjusted for study therapy at discharge (no/yes), sex (male/female), and available cardiovascular risk factor (no/unknown/yes), and age within each stratum as continuous variable.

Age and major hemorrhage after ischemic stroke (Paper II)

Overall, 58,868 patients with a first-ever, non-fatal ischemic stroke and who were discharged alive between 2001 and 2005 were included in the study for Paper II (Figure 4).

Approximately 10% of the patients had had at least one major hemorrhage before index stroke and 5% after index stroke. In the entire cohort, almost half of the hemorrhages were gastrointestinal hemorrhage; one-third was intracranial hemorrhage; and, one-fifth hemorrhages in other locations. However, the 30-day case fatality rate was higher for intracranial events than for gastrointestinal events and hemorrhages in other locations.

The relation between age and major hemorrhages after stroke, considering prescribed antithrombotic therapy, is presented in Figure 6. In patients <85 years, there were no major differences in the unadjusted rates of hemorrhage between patients who were prescribed warfarin or antiplatelet therapy, but the hemorrhage rate was higher in the minority of patients not prescribed antithrombotics.

However, there was no amendment for patients with presumed high bleeding being withheld warfarin and prescribed antiplatelet agents (or no antithrombotics) instead. Hence, the estimated risk of hemorrhage in association with age and previous hemorrhages should be interpreted within each treatment category and not in-between treatment categories. For all categories, the risk of hemorrhage increased for those with a history of hemorrhage before index stroke; for categories including those prescribed antithrombotic therapy, the risk of hemorrhage increased with older age (≥75 years).
The crude risk of hemorrhage within each stratum (previous bleeding and age) is presented in Table 3 in Paper II. However, the estimates did not differ after adjustment for sex, age, and cardiovascular risk factors in the multivariable model (Table 6).

Table 6. Crude and adjusted hazard ratios for hemorrhage after ischemic stroke

<table>
<thead>
<tr>
<th>History of hemorrhages</th>
<th>Warfarin</th>
<th></th>
<th>Antiplatelets</th>
<th></th>
<th>No antithrombotics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>History of hemorrhages</td>
<td>HR</td>
<td>HR</td>
<td>HR</td>
<td>HR</td>
<td>HR</td>
<td>HR</td>
</tr>
<tr>
<td>No</td>
<td>reference</td>
<td></td>
<td>reference</td>
<td></td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.7</td>
<td>1.6</td>
<td>1.8</td>
<td>1.7</td>
<td>1.6</td>
<td>1.7</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75 yrs</td>
<td>reference</td>
<td></td>
<td>reference</td>
<td></td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>≥75 yrs</td>
<td>1.4</td>
<td>1.3</td>
<td>1.8</td>
<td>1.9</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>History of hemorrhage (no)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75 yrs</td>
<td>reference</td>
<td></td>
<td>reference</td>
<td></td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>≥75 yrs</td>
<td>1.3</td>
<td>1.3</td>
<td>1.8</td>
<td>1.9</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>History of hemorrhage (yes)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75 yrs</td>
<td>reference</td>
<td></td>
<td>reference</td>
<td></td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>≥75 yrs</td>
<td>1.4</td>
<td>1.5</td>
<td>1.4</td>
<td>1.4</td>
<td>0.9</td>
<td>0.9</td>
</tr>
</tbody>
</table>

HR=hazard ratio. Adj.=adjusted, se text for details. Numbers in italic indicate a non-significant (p>0.05) result.
Warfarin and the risk of death after cardioembolic stroke (Paper III)

From the cohort of 58,868 patients (Paper II), 20,442 had AF and known antithrombotic therapy and were included in the study for Paper III (Figure 4). Analyses of all-cause mortality was estimated for the entire AF cohort, but analyses of specified causes of death only was possible for 15,864 patients with a complete death certificate and included up till December 31, 2004.

There was an association between warfarin and risk of death. However, the patients prescribed warfarin differed from the patients prescribed antiplatelets, in that they were younger, more often men, and had less comorbid diseases. To address this concern a propensity score for the likelihood of being prescribed warfarin was included in the estimation of the risk of death. Three additional analyses were conducted to test the robustness of the result and to determine the association of warfarin in certain subgroups.

The risk of death was estimated:
1. within 5 subclasses, defined by quintiles of the propensity score (Table 7);
2. in a model adjusted for additional (to antithrombotics) drugs in patients discharged in 2005;
3. in a model stratified on mRS grade (0-2, 3, 4, and 5).

Table 7. Adjusted risk of death for 15,803 patients with atrial fibrillation and ischemic stroke who were prescribed warfarin or antiplatelet therapy, by subclassification on the propensity score for warfarin

<table>
<thead>
<tr>
<th>Subclass</th>
<th>Therapy</th>
<th>n</th>
<th>%</th>
<th>Mean</th>
<th>SD</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>AP</td>
<td>2961</td>
<td>18.7</td>
<td>0.07</td>
<td>0.02</td>
<td>ref</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>199</td>
<td>1.3</td>
<td>0.07</td>
<td>0.02</td>
<td>0.65 (0.54-0.78)</td>
</tr>
<tr>
<td>Q2</td>
<td>AP</td>
<td>2777</td>
<td>17.6</td>
<td>0.13</td>
<td>0.02</td>
<td>ref</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>384</td>
<td>2.4</td>
<td>0.14</td>
<td>0.02</td>
<td>0.48 (0.40-0.57)</td>
</tr>
<tr>
<td>Q3</td>
<td>Warfarin</td>
<td>712</td>
<td>4.5</td>
<td>0.23</td>
<td>0.03</td>
<td>ref</td>
</tr>
<tr>
<td></td>
<td>AP</td>
<td>2449</td>
<td>15.5</td>
<td>0.22</td>
<td>0.03</td>
<td>0.62 (0.54-0.72)</td>
</tr>
<tr>
<td>Q4</td>
<td>Warfarin</td>
<td>1186</td>
<td>7.5</td>
<td>0.35</td>
<td>0.04</td>
<td>ref</td>
</tr>
<tr>
<td></td>
<td>AP</td>
<td>1277</td>
<td>8.1</td>
<td>0.56</td>
<td>0.12</td>
<td>ref</td>
</tr>
<tr>
<td>Q5</td>
<td>Warfarin</td>
<td>1883</td>
<td>11.9</td>
<td>0.62</td>
<td>0.14</td>
<td>0.82 (0.71-0.96)</td>
</tr>
</tbody>
</table>

Subclasses based on quintiles (Q) of the propensity score, AP=antiplatelets, SD=standard deviation, HR=hazard ratio

A propensity score expresses the likelihood for the dependent variable (i.e. prescription of warfarin) to occur, and grades from zero to one. In the subclass with the lowest probability (Q1), only 1.3% received warfarin but
the mean value of the propensity score was the same as for patients prescribed antiplatelets (0.07). The latter indicated the score was valid, as one measurement of validity is that the means should be less than half a standard deviation apart.

The sensitivity and subgroup analyzes were consistent with the original analyzes, thus, warfarin was associated with a decreased risk of death (HR 0.67; 95% CI 0.63-0.71).

The unadjusted rates of fatal recurrent ischemic stroke were considerably lower among patients prescribed warfarin than among patients prescribed antiplatelet agents (Table 3 in Paper III). As age was associated with the prescription of warfarin, the mortality rates stratified for age (<75 and ≥75 years) were analyzed. In patients <75 years, the rate of fatal hemorrhagic stroke did not differ between the two treatment categories; however, in older patients, the rate was lower among those prescribed warfarin than among those prescribed antiplatelet agents.

Rate is the ratio of number of events divided by total person-time. However, patients prescribed warfarin appeared healthier, and might have been able to contribute more person-time than more fragile patients who were prescribed antiplatelet agents. Nevertheless, analyzes of the proportional distribution of mortality (cause of death divided by all deaths), confirmed the lower proportion of fatal ischemic strokes in patients prescribed warfarin (Figure 7). The differences in the proportion of fatal hemorrhagic strokes between patients prescribed warfarin and antiplatelet were not significant.

![Figure 7. Cause of death (%) in 5018 patients with atrial fibrillation and ischemic stroke by antithrombotics and age. For patients prescribed warfarin, the number of patients who died were 176 (<75yrs) and 644 (≥75yrs) and for patients prescribed antiplatelets, the corresponding numbers were 331 (<75yrs) and 3867 (≥75yrs).](image-url)
Warfarin and the risk of hemorrhagic stroke (Paper IV)

Patients (n=7696) with first-ever hemorrhagic stroke in 2006-9 and patients (n=12 790) with first-ever, non-fatal ischemic stroke and discharged with warfarin in 2001-8 were included in the study for Paper IV (Figure 4).

The first part of the study was a case-control study and comprised 7696 hemorrhagic stroke patients (cases) and 14 670 stroke-free controls. Generally, the cases had a higher burden of comorbid diseases than the controls. However, among the warfarin-treated subjects (775 cases and 645 controls), the proportion of comorbid diseases were more evenly distributed (Figure 8). The association between hemorrhagic stroke and known risk factors, such as hypertension, antiplatelet agents and warfarin therapy, was confirmed. Even though warfarin more than doubled the risk of hemorrhagic stroke, the odds ratio did not change with time.

The second part of the study in Paper IV included a cohort study of 12 790 ischemic stroke patients with warfarin therapy. Both the number of patients prescribed warfarin and the number (and the proportion) of AF patients increased during the study period, however, the proportion of patients with warfarin did not increase (Supplemental Table S1 in Paper IV).

At follow-up (≥1 year), the rate per 100 person-years of subsequent hemorrhagic stroke (0.4; 95% CI, 0.3-0.5) and ischemic stroke (3.5; 95% CI, 3.3-3.7) were within the range from RCT. The risk of subsequent hemorrhagic stroke in patients prescribed warfarin did not change when the second period (inclusion 2005-8: follow-up until 2009) was compared with the first period.

Figure 8. Comorbid disease in all subjects (7696 cases, 14 670 controls) and in subjects (775 cases and 645 controls) with warfarin. AF=atrial fibrillation, CHF=heart failure, HT=hypertension, DM=diabetes mellitus, n.s.=not significant.
(inclusion 2001-4: follow-up until 2005) (HR 1.04; 95% CI, 0.73-1.48) nor when comparing the succeeding study years (2002-9) with 2001 (HR 0.98; 95% CI, 0.91-1.06).
Discussion

Discussion of methods

A major strength of register-based studies is the large size of the study populations. However, when data on extensive numbers of patients are collected, detailed information is more difficult to cover. In addition, observational studies are limited to observing associations, without implying causality. However, these associations can be strengthened by their plausibility and consistency with other studies. The validity of a study can be separated into two components: the validity of the inferences drawn as they concern members of the source population (internal validity) and the validity of the inferences as they concern people outside that population (external validity or generalizability). Most violations of internal validity can be classified into three general categories: selection bias, confounding and information bias.

Selection bias

Selection biases are distortions resulting from the procedures used to select study subjects (e.g. stroke patients) and from factors influencing study participation (e.g. follow-up). All hospitals in Sweden admitting patients with acute stroke report to Riks-Stroke. However, estimates on the total number of stroke events in Sweden are uncertain. The numbers of patients discharged from hospital are reported annually per diagnosis to the NPR. Of all acute stroke events recorded in Riks-Stroke and/or in the NPR, 80.6% occur in both registers, 3.3% in Riks-Stroke only, and 16.1% in NPR only. However, observations of the discharge diagnoses imply the stroke numbers are overinflated, because patients with sequelae of previous stroke are sometimes recorded with an acute stroke diagnosis. This means coverage is probably higher than the reported 80–85% estimate.

In the study for Paper I, 20% of the participants were lost at the 3-month follow-up or had incomplete information (regarding functional impairment) on data that were essential for the estimation of mRS-grades. The patients lost to follow-up had similar cardiovascular risk profile as the original cohort. However, they were moderately younger (approximately 10 months) and had a slightly longer period of follow-up (43 days) than patients in the original cohort.
The selection of patients and the outcome was interpreted as having no conditional association, as there was high coverage of stroke patients in Riks-Stroke and similarities between the patients with missing data and the original cohort.

**Confounding**

Bias from pre-exposure selection is considered as a form of confounding.\(^{96}\) Confounders are factors (such as exposures, interventions, treatments) explaining or producing all or part of the measured effect (outcome): i.e. they are associated with the exposure at the same time as they are associated with the outcome. There was probably a bias in the estimates of treatment impact on outcome (death and major hemorrhage). In these studies, patients with expected short survival-time due to stroke severity or other comorbid conditions and patients with presumed high risk of bleeding might have been discharged with a second-line drug or without drug therapy. Although this assumption was indicated in the analyses of patients by discharge treatment (Paper II), it could not be validated due to limited information on contraindications to warfarin, other than history of previous hemorrhage.

To adjust for this confounding by indication, age, sex, cardiovascular risk factors, and functional impairment (as a measure of stroke severity) were included in the outcome analyses, and the analyses were stratified by age (Papers I & II), previous bleeding (Paper II) and functional impairment (Papers I & III). When comparisons are made within appropriate levels of a stratified confounder, the confounder can no longer confound the comparison.

A probability score for exposure (warfarin at discharge) was conducted in a regression model that included the patients’ background characteristics (Paper III). This model provided a propensity score for warfarin, and was used for adjusting the model for estimating the risk of death. However, confounding by indication might have rendered an underestimation of the risks associated with warfarin.

In the case-control study (Paper IV), the controls were matched by sex and age at year of stroke to improve the precision of analyses and avoid confounding of age and sex. However, the match design precluded the possibility of estimating the effect of the matching factor, i.e. the relation of age, sex or year to hemorrhagic stroke could not be calculated. However, through defining an interaction term involving both a risk factor and a matching variable (warfarin*year), the changes in odds ratios across strata can be modeled.\(^{97}\)
Information Bias

Information bias refers to measurement errors in the information needed to estimate an association. Information on hypertension, diabetes and AF was only retrieved from *Riks-Stroke* for the studies in Papers I and IV (cohort), and only from the NPR for the case-control study in Paper IV. However, for the studies in Papers II and III, the information was retrieved from both *Riks-Stroke* and the NPR: this cross-linking of data decreased the amount of information missing in the other studies. As there was still missing data on smoking habits, particular in older patients, the missing data on smoking was included as an independent variable in the outcome analyzes.

Hospitalization was used for the outcome identification of major hemorrhage (Paper II); however, this meant less severe cases might have been missed. Intracranial hemorrhages are always serious events, whereas, the severity of gastrointestinal and other types of bleedings may range from minor to life threatening. In a preliminary analysis, both main and secondary diagnoses of gastrointestinal and other bleedings were included, which resulted in a higher frequency of bleeding events. However, secondary discharge diagnoses of hemorrhages (other than intracranial) do not always reflect major bleeding. Thus, to minimize the potential non-differential misclassification both main and secondary diagnoses of intracranial hemorrhages and only the main diagnosis of bleeding that were gastrointestinal, or at other sites, were included.

Despite these limitations, the patient sample was large, which served to reduce the likelihood of chance findings by high intra-individual variability, and represented, by its diversity, a broad spectrum of ages and clinical characteristics.

General discussion

The increasing age of patients with ischemic stroke negatively influenced the prescription of secondary prevention (except for antiplatelet agents), and to a limited extent, increased the risk of hemorrhage in patients prescribed anti-thrombotic therapy. In addition, there appeared a decreased risk of death in patients prescribed warfarin than in patients prescribed antiplatelet agents, and the risk of warfarin-associated hemorrhagic stroke has not changed during the 2000s.

Secondary prevention after ischemic stroke

Two-thirds of patients with AF did not receive warfarin treatment (Paper I), and this proportion is replicated in other Scandinavian register studies. 

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There are at least two possible explanations for the conservative attitude towards the treatment of elderly patients. First, there is a higher frequency of comorbid diseases among older patients, and this has an impact on life span and complication rates; although there is lack of information in broad patient categories. Second, there is lack of evidence on elderly patients from RCT and hence clear guidelines with respect to older ages. In stroke trials on secondary prevention with warfarin, the mean age is 71 years, and similar results are reported for patients ≥75 years (mean age 82 years). Even so, there is a scarcity of evidence for patients ≥85 years: this age group constituted one-fifth of the cohort (Paper I) and had an increased risk of both complications and stroke.

Major hemorrhage after ischemic stroke

The annualized rate of hemorrhages (first event only) was 2.5% among patients selected for treatment with warfarin and 2.4% among patients selected for antiplatelet therapy (Paper II). Pooled data from 13 RCT on secondary prevention after stroke present a mean risk of major (i.e. requiring hospitalization) hemorrhage of 2.5% per year in patients allocated warfarin therapy and 1.0% per year in patients allocated antiplatelet therapy. Thus, the hemorrhage rate associated with warfarin therapy was in agreement with the RCT, whereas, the rate associated with antiplatelet drugs was more than double. However, the mean age of the cohort in Paper II was approximately ten years higher than the age of patients included in the RCT. The risk of hemorrhage increases with increasing age and accumulated burden of vascular risk factors. This was confirmed by the overall increased rate of hemorrhages in patients ≥75 years who were prescribed antithrombotic therapy (Paper II) and the increase of intracranial hemorrhages in patients ≥85 years prescribed warfarin, and in particular, by the sharp increase of gastrointestinal hemorrhage in all patients ≥65 years (Figure 6). A meta-analysis of 5 RCT (published in January 2012) that included patients with indications for warfarin other than AF, present no significant difference in the risk of major hemorrhages between patients allocated to either warfarin or to antiplatelets.

Fatality after ischemic stroke

The reduced post-stroke mortality associated with warfarin (Paper III), has also been found in observational studies, although there is no evidence from RCT that warfarin reduces mortality in ischemic stroke patients. Even if it is difficult to establish randomized, controlled studies with enough statistical power to provide the evidence, an RCT investigating apixaban have recently identified a reduction in the risk of death from any cause, compared with warfarin in AF patients.
Current guidelines\textsuperscript{43} for stroke recommend anticoagulant therapy as secondary prevention for patients with AF, and increasing age alone is not a contraindication. However, the recommendations stipulate the assessment of the risk-benefit ratio should include comorbid diseases and the patient’s ability to comply with treatment. For patients with contraindications to anticoagulants, antiplatelet agents are recommended as an alternative.\textsuperscript{27,42,44} The underuse of warfarin in favor of antiplatelet therapy (Paper III) could be explained by physicians’ concerns about effectiveness and bleeding risk, and patients preference, with some concerns being misinterpreted as contraindications.

**Warfarin-associated hemorrhagic stroke**

The temporal risk for warfarin-associated hemorrhagic stroke (considered both as a first event and as a subsequent event to an antecedent ischemic stroke) was unchanged (Paper IV).

The increase of warfarin-use was significant among cases, but not among controls: this was expected, as the controls were matched by age (mean age was 71 years) and, by definition, they were stroke-free, implying a healthier sample than found in the general population. The change in warfarin use could be compared with data from the National Board of Health and Welfare: in the public statistical database, the dispense of warfarin among Swedish inhabitants, aged 65 to 74 years, increased from 4.7\% in 2006 to 5.3\% in 2009.\textsuperscript{55} Although other studies report increased use of warfarin,\textsuperscript{100,101} the results on the incidence of warfarin-associated hemorrhagic stroke are contrasting. In a hospital-based study from the USA,\textsuperscript{100} the incidence of warfarin-associated hemorrhagic stroke increased, but in a population-based study from Finland the incidence of warfarin-associated hemorrhagic stroke decreased.\textsuperscript{101} However, neither study analyzed warfarin as a secondary stroke prevention therapy.

The most important difference between primary and secondary stroke prevention studies is the higher risk of recurrent stroke, conferring a 2.5 times increased risk, in secondary prevention.\textsuperscript{44} In the cohort study (Paper IV), the rate of warfarin-associated hemorrhagic stroke after a previous ischemic event was 0.4\% in both periods and reflected “real-life”: this was in the range presented for warfarin in RCT of new anticoagulants.\textsuperscript{61,102} In subgroups of patients with a previous stroke and who are allocated warfarin, the rates of hemorrhagic stroke were 0.45\% per year during safety analyses of ximelagatran\textsuperscript{102} and 0.77\% per year for patients during safety analyses of dabigatran.\textsuperscript{61} In an era of new antithrombotic therapies, it is important to determine, outside of RCT, the risks and benefits of already established drugs.
Antiplatelets

The prescription of antiplatelet agents (which was dominated by the prescription of aspirin), was the only secondary preventive treatment not negatively influenced by increasing age (Paper I), yet, the rate of major hemorrhages after ischemic stroke increased in patients aged ≥75 years (Paper II). In AF patients with ischemic stroke, antiplatelet agents were associated with increased risk of premature death, increased rate of fatal ischemic strokes, and similar rates of fatal hemorrhagic strokes as with warfarin (Paper III). In cases with hemorrhagic stroke and stroke-free controls, the use of antiplatelet agents was associated with an increased risk of hemorrhagic stroke, compared to when antiplatelet agents was not used (Paper IV). The benefits of antiplatelet agents for AF patients can be related to the treatment effects on other vascular diseases, commonly co-existing with AF. The risk of bleeding from use of antiplatelet agents can be considered similar to the risk of bleeding with warfarin use, especially in the elderly. This could explain why apixaban, compared with aspirin, does not increase the risk of bleeding (but substantially reduces the risk of stroke) in AF patients (with a mean age of 70 years) for whom warfarin therapy is contraindicated or unsuitable.

In summary, antiplatelet agents are not required for stroke prevention in patients with ischemic stroke of cardiac origin. Thus, the health care system needs to develop strategies for improving the management of anticoagulant therapy, irrespective of old or new drug.
Conclusions

In patients with ischemic stroke:
• The prescription of warfarin, ACE-inhibitors and statins, but not the prescription of antiplatelet agents, had an inverse relation to increasing age. However, cardiovascular risk factors were prevalent in all ages in addition to the strongest risk factor for stroke (i.e. previous stroke).
• Compared to results from RCT on antithrombotic therapy, the risk of hemorrhage was similar for patients prescribed warfarin and two times greater for patients prescribed antiplatelet agents. The risk of hemorrhage was moderately increased with both older age and previous hemorrhage.

In patients with ischemic stroke and AF:
• The risk of death associated with prescription of warfarin therapy was lower than with prescription of antiplatelet agents, and there was no increase in the rate of fatal hemorrhagic stroke.
• The risk of subsequent warfarin-associated hemorrhagic stroke did not change during the 2000s.

In patients with hemorrhagic stroke and stroke-free controls:
• The risk of warfarin-associated hemorrhagic stroke did not change between 2006 and 2009.

The effect of secondary preventive drugs on outcome demonstrated in this thesis highlights the importance of assessing an individual’s stroke and bleeding risks in stroke prevention.
Future perspectives

Important progress has been made in the management of stroke, both in the acute setting with improved imaging and interventions and in secondary stroke prevention, through the evidence of effectiveness in RCT. A parallel can be drawn with the advance in management of heart diseases, which has led to a substantial decline in mortality from myocardial infarction. However, the classification of stroke subtypes is vital and further effort should be made to classify stroke of unknown cause (cryptogenic stroke).

Cardiovascular research needs to acknowledge both the multifactorial origins of stroke and the multifaceted characteristics of stroke patients. Ischemic stroke of arterial origin has more in common with myocardial infarction than with hemorrhagic stroke, thus, the effects of preventive drugs investigated in particular subtypes of (ischemic) stroke will provide further evidence and associations. For all stroke patients to have personalized health care, the differences between elderly, frail patients with functional impairment before their stroke and the younger, stronger patients needs to be considered.

The aims of Riks-Stroke are to improve the quality of stroke care in Sweden, to follow-up the National Board of Health and Welfare’s guidelines for stroke care and to provide a data source for research. These aims are not contradictory. Future analyses based on Riks-Stroke will be able to report e.g. the prescription rate of old and new anticoagulants for almost all Swedish stroke patients and link this data with other national registers to provide additional information, e.g. adherence to drug prescriptions, future hospitalizations with diagnoses/complications other than stroke, and death. The large number of patients registered in Riks-Stroke provides the opportunity to study sub-groups based on the subtype and origin of stroke, age, sex, and comorbidity.

Even though Sweden is a small country, Riks-Stroke, in combination with other national registers, provides an internationally unique ability for monitoring the management of stroke and the management’s effect on outcome within an entire nation.
Bakgrund

Stroke är en av de vanligaste yttringarna av hjärt-kärlsjukdom. Antalet strokefall beräknas att öka i framtiden eftersom antalet äldre i befolkningen ökar och risken för stroke stiger med stigande ålder. I Sverige drabbas årligen ca 30 000 personer av stroke och av dessa är det ca 23 000 personer som drabbas för första gången. De flesta strokefallen utgörs av infarkter i hjärnan (85 %), orsakade av proppar i hjärnans kärl, oftast som följd av åderförkalkning eller som följd av förmaksflimmer. En mindre del av strokefallen utgörs av blödning, orsakade av bristning i hjärnans (10 %) eller i hjärnhinnornas (5 %) kärl. Såväl akuta som förebyggande åtgärder skiljer sig åt, utifrån typ av stroke (infarkt/blödning), men gemensamt är väsentligen den hand som påverkar blodplättarna, s.k. trombocythämmare. Vid hjärninfarkt orsakad av blodproppar från åderförkalkade kärl rekommenderas läkemedel som påverkar blodplättarna, s.k. trombocythämmare. Vid hjärninfarkt orsakad av blodproppar från hjärtat vid förmaksflimmer rekommenderas i första hand läkemedel som påverkar blodets koagulationsförmåga s.k. antikoagulantia (såsom warfarin) och i andra hand trombocythämmare. Sedan 2011 finns nya antikoagulantia som andrahandsalternativ till warfarin, men de var inte analyserade i studierna för den här avhandlingen. Försäljning av warfarin till den svenska befolkningen i åldern 65-74 år har ökat från 3,7 % till 4,3 % mellan 2006 och 2009.

Randomiserade prövningar kan påvisa läkemedels nytta och risk, men äldre och skörare patienter är sällan inkluderade i dessa prövningar. Observationsstudier, som de som ingår i den här avhandlingen, kan endast visa associationer mellan läkemedel och effekter, inte direkta orsaksamband. Likväl, eftersom vissa patientgrupper är svåra att inkludera i läkemedelsprövningar och dessutom svåra att följa över tid, utgör observationsstudier ett viktigt komplement till randomiserade läkemedelsprövningar.

En angelägen uppgift för hälso- och sjukvård är att genom förebyggande åtgärder och behandling minska de påfrestningar som orsakas av förstagångs- och återinsjuknandet i stroke. Syftet med denna avhandling var att beskriva användning av strokeförebyggande läkemedel och dess effekter, avspeglad genom det nationella kvalitetsregistret för strokesjukvård: RiksStroke. I Sverige finns en lång tradition av nationella register, den första

Resultat

Rekommenderade läkemedel, som syftar till att förhindra återinsjuknande, förskrevs inte alltid till patienter med hjärninfarkt, trots att riskfaktorer för hjärt-kärlsjukdom var vanligt förekommande bland dem. Stigande ålder är en allvarlig riskfaktor för stroke, men visade sig vara associerad med en minskad förskrivning (Arbete I). Efter en hjärninfarkt förekom, i jämförelse med randomiserade läkemedelsprövningar, allvarliga blödningar i dubbel omfattning hos patienter förskrivna trombocythämmare (2,4 % per år) och i liknande omfattning hos patienter förskrivna warfarin (2,5 % per år). Ålder ≥75 år och tidigare allvarlig blödning var associerade med en måttlig ökad risk för ny blödning (Arbete II).


Behandling med, jämfört med utan warfarin var associerat med dubblad risk för förstagångsinsjuknade i hjärnblödning. Risken har inte ändrats under 2006 till 2009, trots ökad försäljning av warfarin i Sverige under denna period (Arbete IV, fall-kontroll).

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