Recurrent stroke
Risk factors, prevention and prognosis

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Umeå University 2016

Responsible publisher under Swedish law: the Dean of the Medical Faculty

ISBN: 978-91-7601-579-7
ISSN: 0346-6612
New Series No: 1847
Cover Illustration: Emma Korsár
Electronic version available at http://umu.diva-portal.org/
Printed by: Print & Media
Umeå, Sweden 2016

”That boulder did what it was there to do. Boulders fall. That’s their nature. It did the only natural thing it could do.”
Aron Ralston, Between a rock and a hard place

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Abstract

Background Many risk factors for stroke are well characterized and might, at least to some extent, be similar for first-ever stroke and for recurrent stroke events. However, previous studies have shown heterogeneous results on predictors and rates of stroke recurrence. Patients who survive spontaneous intracerebral hemorrhage (ICH) often have compelling indications for antithrombotic (AT) treatment (antiplatelet (AP) and/or anticoagulant (AC) treatment), but due to controversy of the decision to treat, a large proportion of these patients are untreated. In the absence of evidence from randomized controlled trials (RCTs), there is need for more high- quality observational data on the clinical impact of, and optimal timing of AT in ICH survivors. The aims of this thesis were to assess time trends in stroke recurrence, to determine the factors associated with an increased risk of stroke recurrence – including socioeconomic factors – and to determine to what extent ICH survivors with and without atrial fibrillation (AF) receive AT treatment and to determine the optimal timing (if any) of such treatment.

Methods The population-based Monitoring Trends and Determinants of Cardiovascular Disease (MONICA) stroke incidence register was used to assess the epidemiology and predictors of stroke recurrence after ischemic stroke (IS) and ICH from 1995 to 2008 in northern Sweden. Riksstroke, the Swedish stroke register, linked with the National Patient Register and the Swedish Dispensed Drug Register, made it possible to identify survivors of first-ever ICH from 2005 to 2012 with and without concomitant AF to investigate to what extent these patients were prescribed AP and AC therapy. The optimal timing of initiating treatment following ICH in patients with AF 2005–2012 was described through separate cumulative incidence functions for severe thrombotic and hemorrhagic events and for the combined endpoint "vascular death or non-fatal stroke". Riksstroke data on first-ever stroke patients from 2001 to 2012 was linked to the Longitudinal Integration Database for Health Insurance and Labour market studies to add information on education and income to investigate the relationship between socioeconomic status and risk of recurrence.

Results Comparison between the cohorts of 1995–1998 and 2004–2008 showed declining risk of stroke recurrence (hazard ratio: 0.64, 95% confidence interval (CI): 0.52-0.78) in northern Sweden. Significant factors associated with an increased risk of stroke recurrence were age and diabetes. Following ICH, a majority (62%) of recurrent stroke events were ischemic. The nationwide Riksstroke study confirmed the declining incidence, and it further concluded that low income, primary school as highest attained level

of education, and living alone were associated with a higher risk of recurrence beyond the acute phase. The inverse effects of socioeconomic status on risk of recurrence did not differ between men and women and persisted over the study period.

Of Swedish ICH-survivors with AF, 8.5% were prescribed AC and 36.6% AP treatment, within 6 months of ICH. In patients with AF, predictors of AC treatment were less severe ICH, younger age, previous anticoagulation, valvular disease and previous IS. High CHA_2DS_2-VASc scores did not seem to correlate with AC treatment. We observed both an increasing proportion of AC treatment at time of the initial ICH (8.1% in 2006 compared with 14.6% in 2012) and a secular trend of increasing AC use one year after discharge (8.3% in 2006 versus 17.2% in 2011) ($p<0.001$ assuming linear trends). In patients with high cardiovascular event risk, AC treatment was associated with a reduced risk of vascular death and non-fatal stroke with no significantly increased risk of severe hemorrhage. The benefit appeared to be greatest when treatment was started 7–8 weeks after ICH. For high-risk women, the total risk of vascular death or stroke recurrence within three years was 17.0% when AC treatment was initiated eight weeks after ICH and 28.6% without any antithrombotic treatment (95% CI for difference: 1.4% to 21.8%). For high-risk men, the corresponding risks were 14.3% vs. 23.6% (95% CI for difference: 0.4% to 18.2%).

Conclusion Stroke recurrence is declining in Sweden, but it is still common among stroke survivors and has a severe impact on patient morbidity and mortality. Age, diabetes and low socioeconomic status are predictors of stroke recurrence. Regarding ICH survivors with concomitant AF, physicians face the clinical dilemma of balancing the risks of thrombosis and bleeding. In awaiting evidence from RCTs, our results show that AC treatment in ICH survivors with AF was initiated more frequently over the study period, which seems beneficial, particularly in high-risk patients. The optimal timing of anticoagulation following ICH in AF patients seems to be around 7–8 weeks following the hemorrhage.

Original articles

This thesis is based on the following articles, which will be referred to in the text by the corresponding Roman numerals (**I-IV**):

I: Pennlert J, Eriksson M, Carlberg B, Wiklund PG. Long-term risk and predictors of recurrent stroke beyond the acute phase. *Stroke*. 2014;45:1839-1841.

II: Pennlert J, Asplund K, Carlberg B, Wiklund PG, Wisten A, Åsberg S, Eriksson M. Antithrombotic treatment following intracerebral hemorrhage in patients with and without atrial fibrillation. *Stroke*. 2015; 46:2094-2099.

III: Pennlert J, Overholser R, Asplund K, Carlberg B, van Rompaye B, Wiklund PG, Eriksson M. Optimal timing of anticoagulant treatment following intracerebral hemorrhage in patients with atrial fibrillation. Submitted.

IV: Pennlert J, Asplund K, Glader EL, Norrving B, Eriksson M. Socioeconomic status and the risk of stroke recurrence. Persisting gaps observed in a nationwide Swedish study 2001-2012. Submitted.

Abbreviations

AC	Anticoagulant
ADL	Activities of daily living
AF	Atrial fibrillation
AP	Antiplatelet
ASA	Acetylsalicylic acid
AT	Antithrombotic
ATC	Anatomical Therapeutic Chemical
CAA	Cerebral amyloid angiopathy
CDR	Cause of Death Register
$CHADS_2$	Acronym for Congestive heart failure, Hypertension, Age, Diabetes, previous Stroke/TIA
CHA_2DS_2-VASc	Acronym for Congestive heart failure, Hypertension, Age, Diabetes, previous Stroke/TIA, VAScular disease
CI	Confidence interval
CIF	Cumulative incidence function
DALYs	Disability-adjusted life years
HAS-BLED	Acronym for Hypertension, Abnormal liver/renal function, Stroke, major Bleeding history (or anemia, predisposition to bleeding), Labile International Normalized Ratio (INR), Elderly (age >= 65), Drug therapy (concomitant therapy such as AP, NSAID – non-steroidal anti-inflammatory drugs)/excessive alcohol intake
HR	Hazard ratio
ICD	International Classification of Diseases
ICH	Intracerebral hemorrhage
INR	International Normalized Ratio
IS	Ischemic stroke
IPR	Inpatient Register (part of the NPR)
K-M	Kaplan–Meier
LISA	Longitudinal Integration Database for Health Insurance and Labour Market Studies
MI	Myocardial infarction
MONICA	Monitoring of Trends and Determinants of Cardiovascular Disease
NOACs	Non-vitamin K antagonist oral anticoagulants
NPR	National Patient Register
PAR	Population attributable risk
PH	Proportional Hazard
PPV	Positive predictive value

RCT	Randomized controlled trial
RLS	Reaction Level Scale
SAH	Subarachniodal hemorrhage
SES	Socioeconomic status
SPDR	Swedish Prescribed Drug Register
STA	Swedish Tax Agency (Folkbokföringen)
TIA	Transient ischemic attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment (stroke classification)
VTE	Venous thromboembolism
WHO	World Health Organization

Populärvetenskaplig sammanfattning

Bakgrund

Av ca 30,000 strokeinsjuknanden per år i Sverige utgör ca 25 % återinsjuknanden. Givet en åldrande befolkning, och i skenet av att dödligheten i sjukdomen minskat, förväntas antalet stroke-överlevare i Sverige öka i framtiden. Grovt kan stroke indelas i hjärninfarkter (som orsakas av ocklusion i flera, eller något av hjärnans blodkärl) och spontana hjärnblödningar. Många riskfaktorer för stroke är relativt väl kända och kan antas vara i princip desamma för förstagångs-stroke som för återinsjuknanden, men populationsbaserad kunskap om vilka faktorer som gör vissa individer speciellt utsatta för risken att återinsjukna saknas. Få studier har intresserat sig för hur socioekonomiska skillnader (t ex olika utbildnings- och inkomstnivåer) påverkar risken att återinsjukna och resultaten från de små studier som finns är motstridiga.

Vad gäller läkemedelsbehandling av strokepatienter för att förebygga återinsjuknanden finns gott vetenskapligt underlag för blodtryckssänkande läkemedel efter både hjärninfarkt och hjärnblödning och för blodfettssänkande läkemedel och proppförebyggande (trombocythämmande) behandling till patienter som överlevt hjärninfarkt. Enligt gällande riktlinjer skall patienter som genomgått en hjärninfarkt och har kroniskt eller paroxysmalt förmaksflimmer behandlas med blodförtunnande läkemedel (antikoagulantia). Idag har ca 30 % av patienterna som insjuknar i hjärninfarkt förmaksflimmer. Förebyggande behandling efter hjärnblödning kompliceras av att patienter som överlevt hjärnblödningar å ena sidan löper risk för att återinsjukna i en ny hjärnblödning, å andra sidan inte sällan har samtidig indikation för trombocythämmande eller blodförtunnande behandling, t ex tidigare hjärtinfarkt eller förmaksflimmer. Det saknas idag vetenskapligt väl underbyggda riktlinjer för hur läkare skall hantera detta kliniska dilemma.

Målsättning

Syftet med detta avhandlingsarbete var att undersöka risken att återinsjukna i stroke och redogöra för vilka faktorer som medför ökad risk, att kartlägga hur stor andel patienter som ordineras antikoagulantia eller trombocythämmande läkemedel efter hjärnblödning, och slutligen att studera utfallet och den eventuellt optimala insättningstiden (vad gäller risk/nytta) av sådan behandling bland patienter, med förmaksflimmer, som överlevt hjärnblödning.

Metoder och Resultat

Alla delstudier i denna avhandling är registerbaserade observationsstudier.
I en studie av 6,700 patienter som överlevt en första stroke i Norr- och Västerbotten och registrerats i det populationsbaserade MONICA stroke incidensregistret mellan åren 1995–2008 visade vi en 36 % minskad risk att återinsjukna bland patienter i den senaste tidsperioden, jämfört den första. I övrigt fann vi att äldre patienter och patienter med diabetes löpte ökad risk att återinsjukna. I en studie, baserad på nationella data från Riksstroke, som omfattade 168,295 patienter, såg vi även att patienter med lägre utbildnings- och inkomstnivå samt ensamboende löpte större risk att återinsjukna i stroke. Sambandet mellan låg socioekonomisk status och högre risk att återinsjukna var liknande bland män och kvinnor och minskade inte över tid.

Andelen patienter som överlevt en hjärnblödning med samtidigt förmaksflimmer har ökat över tid och av alla patienter med hjärnblödning stod ca 40 % på antingen trombocythämmande eller blodförtunnande behandling vid tiden för insjuknandet. Patienter med förmaksflimmer som överlevt hjärnblödning och, efter utskrivning från sjukhus, fick behandling med antikoagulantia var yngre, hade oftare en historik av tidigare hjärninfarkt, stod i större utsträckning på antikoagulantia vid tidpunkten för hjärnblödningen, led oftare av samtidig hjärtklaffsjukdom och hade mindre allvarliga hjärnblödningar jämfört de som inte fick behandling. Bland flimmerpatienterna sågs också en trend att behandling med antikoagulantia efter hjärnblödning har blivit vanligare över tid.

Behandling med antikoagulantia var associerad med en minskad risk för den kombinerade utfallsvariabeln vaskulär död och icke-fatal stroke bland högriskpatienter med förmaksflimmer som överlevt hjärnblödning. Det optimala tidsintervallet för insättning av behandling tycktes vara ca 7–8 veckor efter hjärnblödningen för att maximera nyttan och minimera riskerna med behandlingen.

Diskussion och slutsatser

I delstudierna till denna avhandling har vi följt svenska stroke-patienter över en 18-årsperiod (1995–2012). Under denna tid har stora förbättringar inom den svenska strokevården skett, fler får rätt förebyggande behandling efter stroke (såsom blodtryckssänkande behandling och därtill blodfettssänkande och antitrombotisk behandling efter hjärninfarkter), en växande andel har under studietiden vårdats på stroke-enhet och även tillgången till akutbehandling i form av propplösande läkemedel efter hjärninfarkt har

ökat. Dessutom ser man, på befolkningsnivå, positiva trender vad gäller generella riskfaktorer för hjärt-kärlsjukdom, såsom mindre rökning, lägre blodfetter och lägre blodtrycksnivåer. Allt detta förklarar säkerligen åtminstone delvis våra fynd att risken att återinsjukna i stroke har minskat över tid. Det finns dock anledning att intensifiera förebyggande åtgärder i vissa utsatta grupper. Patienter med diabetes och äldre personer löper större risk att återinsjukna, liksom de i socialt underprivilegierade grupper. Även de som bor ensamma löper större risk att återinsjukna.

Vad gäller det kliniska dilemmat kring antitrombotisk behandling efter hjärnblödning, där patienten å ena sidan löper ökad risk att drabbas av en ny hjärnblödning och å andra sidan ofta har risk för blodproppar, fann vi att allt fler som insjuknar i hjärnblödning står på blodförtunnande behandling vid insjuknandet. Trots avsaknad av evidens har också läkare blivit mer benägna att behandla patienter med blodförtunnande behandling efter hjärnblödning under de år (2005–2012) vi studerat. Denna kliniska praxis har dock visat sig vara till godo för de flesta patienter vi observerat med samtidigt förmaksflimmer. Den optimala tiden för insättning av blodförtunnande behandling till denna patientgrupp för att minimera risk och maximera nyttan tycks vara ca 7–8 veckor efter hjärnblödningen. Den bästa behandlingsstrategin efter hjärnblödning för de patienter som har stark indikation för blodförtunnande läkemedel behöver studeras i randomiserade prövningar.

Framtida forskning

Trots en glädjande trend att återinsjuknande i stroke över studietiden har minskat, så finns särskilt utsatta grupper och fortsatt forskning rörande insatser för att optimera sekundärprevention för dessa borde prioriteras. Vad gäller socioekonomiska faktorers betydelse för återinsjuknanderisk behöver våra fynd verifieras även i andra länder, där den socioekonomiska sammansättningen av populationen ser annorlunda ut. I skenet av en åldrande befolkning, med ökande andel förmaksflimmer i populationen och ökad användning av blodförtunnande behandling i klinisk praxis över tid, behöver randomiserade prövningar och observationsstudier komplettera varandra för att avgöra den optimala farmakologiska behandlingsstrategin efter hjärnblödning.

Aims

The general aims of this thesis were to investigate rates and predictors of stroke recurrence and to further explore the distribution, predictors, risk-benefit, and the optimal timing (if any) of antithrombotic therapy following intracerebral hemorrhage.

Specific aims

I: To explore the rates of, and risk factors for stroke recurrence in the population-based Northern Sweden MONICA stroke incidence registry from 1995 to 2008.

II: To determine the extent and predictors of initiation of antithrombotic treatment (antiplatelet therapy and anticoagulant therapy) following intracerebral hemorrhage in Sweden.

III: To provide observational data on the risk/benefit of antithrombotic treatment following intracerebral hemorrhage in patients with concomitant atrial fibrillation and (for beneficial treatment strategies) to determine the optimal timing of such treatment.

IV: To assess the relationship between socioeconomic status and the risk of stroke recurrence in a nationwide study from 2001 to 2012 and to assess temporal trends in the possible associations.

Introduction

In 2010, stroke was ranked as the second leading cause of death worldwide, accounting for around 10% of all deaths[1], and it was ranked as the third most common cause of disability-adjusted life-years (DALYs) globally[2]. There is a substantial geographical difference in stroke burden. Stroke is disproportionally affecting low-income and middle-income countries and the discrepancy is worsening. While age-standardized incidence rates and case fatality rates in high-income countries have decreased, the converse has been shown for low- and middle-income countries.[3] Assuming that the growth and ageing of populations and that current trends in stroke incidence, mortality and DALYs will continue, by 2030 there will be almost 70 million stroke survivors, 12 million stroke deaths and more than 200 million DALYs lost globally each year.[3]

Stroke and stroke recurrence in Sweden

Every 17 minutes someone suffers from a stroke in Sweden.[4] After ischemic heart disease and cancer, stroke is the third leading cause of death[5] and a leading cause of acquired disability among adults[6]. Approximately 30,000 persons in Sweden have a stroke each year and patients surviving an initial stroke are known to be at greater risk of further strokes compared to the general population[7]. Between 23% and 30% of all Swedish stroke events are recurrent events[8]. Recurrent stroke is an important preventable risk factor for poor long-term outcome (death, institutionalization or disability)[9], and recurrent stroke events are also, apart from being more disabling and fatal, frequently ischemic and more costly in nature than first-ever stroke events[10, 11]. Given an ageing population and lower stroke fatality-rates, the absolute numbers of stroke survivors could be expected to also increase in Sweden, accentuating the need for greater awareness about, and refined measures to prevent, stroke recurrence.

Stroke definition and classification

Health classifications are a core responsibility of the World Health Organization (WHO) of which the International Statistical Classification of Diseases and Related Health Problems (ICD) is historically the most important. The current WHO definition (version ICD-10) of stroke is:

> *"rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin"*[12]

Stroke events are either ischemic or hemorrhagic[13], based on their underlying pathology. In ischemic stroke (IS), which accounts for approximately 80% of all strokes[13], the obstruction of blood-flow is caused by cerebral vessel occlusion. In hemorrhagic stroke, the spontaneous rupture of cerebral blood vessels cause bleeding into the brain parenchyma or the ventricular system (intracerebral hemorrhage, ICH), or into the subarachnoidal space. Subarachnoidal hemorrhages (SAH) account for approximately 5% of all stroke events and are not included in the study populations of this thesis. Hence, the term "hemorrhagic stroke" in this work is equivalent to intracerebral hemorrhage (ICH). Subdural and epidural hematomas and traumatic ICH are not included in the stroke definition.[14] The diagnosis of a transient ischemic attack (TIA) is closely related to that of stroke. The classic definition of TIA is:

> *"a sudden, focal neurologic deficit that lasts for less than 24 hours, is presumed to be of vascular origin, and is confined to an area of the brain or eye perfused by a specific artery"*[15]

The definition of TIA has been challenged in recent years mainly due to major advances in neuroimaging and pathophysiology over the last decades.[16] In the upcoming WHO ICD-version, ICD-11, the definition of TIA is suggested to be redefined as "a transient episode of acute focal neurological dysfunction caused by focal ischemia of the brain or retina, *without demonstrated acute infarction* in the clinically relevant area of the brain. Symptoms should resolve completely within 24 hours."[17] Definitions of TIA and stroke relevant to this thesis are, however, those restricting the TIA-diagnosis to symptoms lasting less than 24 hours and the current WHO definition of stroke given above. The definition of *unspecified stroke* events within this thesis includes cases where no neuroimaging had taken place, i.e. it was not possible to distinguish between IS and ICH.

IS and ICH subtypes and risk of recurrence

As mentioned above, there have been major advances in neuroimaging and pathophysiology over the last four decades and for the main stroke types (IS and ICH) several sub-classification schemes have been proposed during this time. For IS, the most widely used sub classification scheme is the Trial of Org. 10172 in Acute Stroke Treatment (TOAST) classification dividing IS into a) *large-artery atherosclerosis*, b) *cardioembolism*, c) *small-vessel occlusion*, d) *other determined causes* and e) *undetermined causes*.[18] In terms of risk of stroke recurrence, large-artery atherosclerosis, which

accounts for around 15%–20% of cerebral infarctions[19], is the IS subtype that is associated with the highest risk of early recurrence.[20, 21] Cardioembolic strokes (accounting for 14%–30% of IS), are most often caused by atrial fibrillation (AF), and are associated with both a high risk of both early and long-term recurrence.[22] Cardioembolic stroke caused by AF is generally the most severe IS subtype associated with higher mortality and disability rates than other types of brain infactions.[23]

Also for ICH, the risk of recurrence depends on the underlying pathology.[24] ICH location is often used as a proxy for underlying cause[25] where most ICHs in the deep parts of the brain (thalamus, basal ganglia) or brainstem territories (*"deep ICH"*) are likely caused by hypertensive vasculopathy while superficially located, *"lobar ICH",* is often associated with cerebral amyloid angiopathy (CAA).[24] CAA refers to the deposition of β-amyloid in the vessel walls of small and mid-sized arteries (and less frequently in veins) of the cerebral cortex and leptomeniges.[26] ICH is the probably the most recognized associated clinical phenotype of CAA. The reported annual recurrence rates for lobar hemorrhages vary between 3% and 14%[27] while recurrence rates following deep ICH have been reported to be around 2% per year[28].

Stroke risk factors

The term "risk factor" is one of the most central terms in epidemiological research, and it is defined as any patient characteristic, attribute or exposure that is independently associated with an increased risk of developing disease or injury[29]. Stroke risk factors are either classified as either modifiable or non-modifiable[13].

Non-modifiable risk factors for stroke include advanced age, which is associated with increased stroke incidence rates in both men and women, and increased risk for both IS and ICH.[30] Male sex increases the age-adjusted risk of stroke, except in the oldest age groups where the risk difference tends to decrease.[31, 32] Women, however, tend to suffer more severe strokes than men[31, 33, 34] which may partly be explained by the proportionally higher prevalence of cardioembolic stroke in women, while large artery atherosclerosis and small vessel occlusion are proportionally more common in men.[31] Several genetic factors have been proposed to signal increased risk of stroke, and stroke genetics is rapidly becoming an integral part also in studies of outcome and pharmacogenetics.[35]

The effects of *modifiable risk factors* may be reduced by treatment and life-style interventions. In 2010, the first results from a massive global case-control study, Interstroke, were published.[36] The overall objective of

Interstroke was to describe and quantify the contribution of common and potentially modifiable risk factors for stroke. The main finding was that 10 modifiable vascular risk factors are associated with approximately 90% of the risk of population attributable risk (PAR) of stroke, a finding that was confirmed in a larger-scale phase of the Interstroke Study presented in 2016.[36, 37] Hypertension is the most important risk factor for all stroke subtypes, and it is a more potent risk factor for ICH than for IS. AF is associated with an increased risk of IS in all regions assessed, but is of greater importance in Western Europe, North America and Australia than in China and South Asia (the PAR in Western Europe is 17.1%, meaning that an estimated 17.1% of the total stroke burden would be eliminated in the region if AF was eliminated). Other important stroke risk factors are physical inactivity, poor diet, obesity, smoking, other cardiac causes, diabetes, heavy alcohol intake, stress and dyslipidemia.[37]

Atrial fibrillation

AF is an independent risk factor for IS, increasing the risk by about five fold,[38] and around 30% of all patients with IS suffer from the condition.[39-45] AF is also the most common indication for anticoagulation[46] whereas ICH is the most feared and deadly complication of AC treatment[47]. In Sweden, AF affects at least 2,9% of the adult population (≥20 years) and the prevalence of AF increases dramatically with age, from about 1% among 50 year-olds to 14% at 85 years[48]. Among Swedish IS patients above 85 years of age, the proportion of AF is as high as 46.6%.[39] The pathophysiology behind the thrombogenesis in AF is complex and remain only partly understood[49], but it is clear that the risk of stroke is not evenly distributed in the AF population.

Warfarin (a vitamin K antagonist) has historically been the most frequently used oral anticoagulant (AC) drug in AF to prevent stroke in Sweden.[50] Warfarin reduces the risk of IS by approximately 60%.[51] With platelet inhibitors – antiplatelets (APs) – this reduction is about 20%–25%.[51, 52] In current European guidelines for the management of AF, AP therapy has almost no place in the prevention of IS in AF patients, and current guidelines state that acetylsalicylic acid+clopidogrel should only be considered an alternative to AC in situations where patients refuse AC treatment or cannot tolerate AC for reasons unrelated to bleeding.[53]

Since 2011, somewhat overlapping the study-periods of papers II and III, new AC agents that do not require laboratory monitoring have been increasingly used in AF[50], including dabigatran[54], rivaroxaban[55] and apixaban[56]. Among patients included in papers II and III, however, an

overwhelming majority was subscribed warfarin. Randomized controlled trials (RCTs) of the new non-vitamin K antagonist oral anticoagulants (NOACs) have shown the agents to be associated with a lowered risk of ICH compared to warfarin[57], but an increased risk of gastrointestinal hemorrhage has been reported with some NOACs[58, 59]. Importantly, extra-cranial hemorrhages (e.g. gastrointestinal hemorrhage, epistaxis and hematuria) leads to disability or death in only 3% of the cases, whereas ICH leads to death or disability in 76% of the cases.[60] Also of relevance to this thesis, none of the recent RCTs of NOACs in AF included patients with previous ICH, all protocols defined a "history of intracranial bleeding" as an exclusion criterion.[54-56, 61] In 2015, NOACs following IS in patients with AF constituted 63% of prescriptions of AC for secondary prevention, a dramatic increase from 2014 (34%)[62].

Risk stratification scores

The risk of IS in patients with AF depends on other underlying conditions such as age, sex, history of diabetes and congestive heart failure. The risk stratification score of $CHADS_2$[63] was introduced in 2001 due to this heterogeneity of the AF population in terms of IS risk. In this risk stratification scheme, one point each is earned for the presence of congestive heart failure, hypertension, age ≥75 years, diabetes and two points are earned for previous stroke or TIA. In 2010, the CHA_2DS_2VASc-score[64] was developed as a refinement of $CHADS_2$ primarily to improve the risk classification in low-risk patients. In addition to the risk factors included in $CHADS_2$, CHA_2DS_2-VASc also includes vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), female sex, age ≥65 years and a doubling of score points for age ≥75 years. According to current European guidelines on the management of AF[53], CHA_2DS_2-VASc is recommended for stroke risk stratification, by which patients with CHA_2DS_2-VASc scores of 0 (including women with no other concurrent stroke risk factors) are not recommended AT treatment and patients with CHA_2DS_2-VAsc scores of ≥2 are recommended oral ACs. Importantly, risk stratifications scores for IS/systemic embolism in AF patients have not been validated in patients with previous ICH.

To predict the risk of bleeding when considering AC treatment, a commonly used risk stratification score is HAS-BLED.[65] The scoring system was introduced in 2010 and according to this scheme, 1 point is awarded for systolic blood pressure >160, abnormal renal or hepatic function, previous stroke, history of bleeding or predisposition, labile international normalized ratio, age > 65 years, excessive alcohol use and concomitant use of other

drugs (AP or non-steroidal anti-inflammatory drugs). Current European AF guidelines recommend the use of HAS-BLED to assess bleeding risk and caution, as well as efforts to correct the potentially reversible risk factors, in patients with HAS-BLED scores of ≥3.[53]

Anticoagulant treatment in Swedish AF patients

According to a report from the National Board of Health and Welfare published in 2014, a clinically reasonable target level for AC treatment in AF patients with risk factors for IS (i.e. CHA_2DS_2-VASc ≥2 points or with the presence of mechanical heart valve prosthesis or mitral stenosis) is 80%. Not all patients are eligible for treatment because of contraindications and bleeding risk. In order to reach the target level of 80%, an additional 8,700 AF patients with IS risk would annually have to start AC treatment.[66] In women and in patients >80 years, the extent of undertreatment is particularly severe.[67]

Socioeconomic status and stroke

According to the Swedish Health and Medical Service Act, the objective of the Swedish healthcare system is *"to assure the entire population good health and care on equal terms"*. Health care is to be provided with respect for every individuals´ equal value and those with the greatest needs should be given the highest priority.[68] As mentioned above, there is today high-quality evidence that stroke disproportionally affects low- and middle-income countries[3], but there are also socioeconomic disparities in several aspects of the burden of stroke within high-income countries. Several recent studies have been focused on the effects of socioeconomic status (SES) on access to stroke care in Sweden. They report inequalities in reperfusion therapy[69], in access to stoke unit care during the implementation phase[70] and in prescriptions of statins following IS[71]. Long-term outcome has also been investigated, and low SES is associated with reduced long-term survival[72], an increased risk of suicide[73], and a decreased likelihood to return to work[74] following stroke.

Rates and predictors of recurrent stroke

In a meta-analysis by Mohan et al, including 13 studies, the authors demonstrated wide variations in reported cumulative risk of recurrent stroke up to 10 years after first stroke, and they observed significant heterogeneity at all time-points. The pooled cumulative risk of stroke recurrence was 11.1% at 1 year, 26.4% at five years and 39.2% at 10 years following a first-ever

stroke. A contributing cause of the observed heterogeneity might be that both hospital-based and population-based studies were included.[75]
There has also been a call for more population-based data regarding predictors of stroke recurence[76]. Previous studies report advanced age[77], diabetes mellitus[78, 79], hemorrhagic stroke[78], history of TIA[80, 81], hypertension[80, 82, 83], male sex[80], previous myocardial infarction (MI)[83], high alcohol consumtion[82], dementia[77] and AF[80, 81, 83] as significant risk factors. A recent study also demonstrated an elevated risk of stroke recurrence in patients with siblings with stroke histories or relatives with early-onset stroke.[84] A genetic risk factor for the recurrence of lobar ICH is the apolipoprotein E genotype[85], which has been suggested to reflect its role in CAA.[86]

Socioeconomic status and stroke recurrence

To date three studies have investigated the relationship between SES and risk of stroke recurrence, returning somewhat conflicting results.[83, 87, 88] A Swedish study reported an increased risk of recurrence with lower income in women, but the association was not seen in men.[87] An Italian study, however, found a tendency toward an increased risk of IS recurrence in men of lower SES (evaluated by using a small area socioeconomic position index), but not in women[88]. Finally, a UK study, adjusting for cardiovascular risk factors, found no overall association between risk of stroke recurrence and the socioeconomic variables that were assessed[83]. Common to these three previous studies is that they were relatively small with low statistical power to ascertain significant differences in subgroup analyses.

National guidelines for secondary prevention

The Swedish national guidelines for stroke care are currently under revision. Relevant to this thesis are previously updated versions from 2000, 2005 and 2009.[89-91] For secondary prevention of stroke, the guidelines do not differentiate between men and women or between different ethnic or socioeconomic groups and also aim to ensure that all patients are treated equally irrespective of where they live. See table 1 for recommended drug treatments following IS and ICH (in patients with and without AF). Recommendations on drug therapy following stroke are generally the same in both the 2005 and 2009 guidelines. However, NOACs were introduced in a 2011 complement to the 2009 guidelines[92], and statins (lipid-lowering treatment) were given higher priority in 2009 compared to 2005 .

Table 1. Drugs recommended for secondary prevention in stroke patients according to current Swedish guidelines for Swedish stroke care. (* ACE-inhibitors, ARBs, diuretics, beta blockers or calcium channel blockers. ** Acetylsalicylic acid (ASA), ASA+dipyramidole or clopidogrel)

	Following ICH	Following IS	Following IS with AF	Following ICH with AF
Antihypertensive treatment*	x	x	x	x
Lipid-lowering treatment		x	x	
Antiplatelet treatment**		x		
Anticoagulant treatment			x	

The current national guidelines on secondary prevention also include recommendations on lifestyle changes, multidisciplinary rehabilitation, and in selected cases, removal of carotid stenosis by carotid endarterectomy. None of these are discussed further within this thesis.

Antithrombotic therapy following ICH

ICH is associated with a higher case-fatality than IS and with warfarin-associated ICH, the risk of disability and death is substantially higher.[93, 94] The American and European guidelines have given somewhat contradictory recommendations whether to resume AC treatment after warfarin-associated ICH over the years, and both guidelines strongly emphasize the need for RCTs.[95-98] In current Swedish guidelines, nothing is written on the topic. The lack of consensus is probably attributable to the sparse scientific background material. Table 2 presents an overview of observational studies investigating outcome after initiating or resuming AT (AC or AP) treatment following ICH[99-111]. Today there is emerging observational evidence that AC reduces the risk of thrombotic events and all-cause mortality, also in ICH-survivors, but the optimal timing of initiating such treatment was not explored in these studies.[109, 111] The largest retrospective study, examining the optimal timing of reinitiating treatment, by Majeed and colleagues, included three tertiary centers and 234 patients with warfarin-associated intracranial hemorrhage (also including traumatic hemorrhages and SAHs), of which 130 were primary ICH cases. A total of 59 patients resumed AC treatment (23 following ICH), and the authors concluded that resumption of treatment should be delayed by 10 to 30 weeks to avoid the early high-risk period for recurrent hemorrhage.[105] In contrast, a systematic review detailing 492 patients suggested that anticoagulation in high-risk patients might be restarted as early as three days from the time of intracerebral bleedings, but the authors emphasize the limitations inherent in the analyzed studies.[103] In the absence of RCTs on the topic of AC following ICH, current clinical practice seems based on a combination of anecdotal experience, pathophysiological constructs and expert opinion. Not surprisingly, previously reported management recommendations from seven experts from three different continents varied widely and there was no general agreement regarding subsequent anticoagulation in patients with AF who survived warfarin-associated ICH.[112]

Table 2. Overview of studies of antiplatelet (AP) and anticoagulant (AC) treatment following ICH. (AT – antithrombotic, trtmt – treatment).

Author (year)	Type of study	Number of patients	Separate analysis of AF patients	Main Findings
Butler (1998)[99]	Single-center cohort study	AC 23 AP or no AT trtmt 22	No	Low risk of hemorrage after AC resumption
De Vleeschouver (2005)[100]	Single-center cohort study	AC 23 AP or no trtmt 85	No	Low risk of hemorrhage after AC resumption
Viswanathan (2006)[101]	Register-study	AC 0 AP 46 No trtmt 161	Yes	No increased risk of hemorrhage after AP
Claassen (2008)[102]	Single-center cohort study	AC 23 AP or no AT trtmt 25	No	Risk-benefit for hemorrhagic/ ischemic event = 0
Hawryluk (2010)[103]	Systematic review of case reports/case series	AC 492	No	In high risk patients, AC may be resumed after 72 hours, but authors emphasize limitations
Flynn (2010)[104]	Register-study	AC 15 AP 120 No AT trtmt 282	No	No increased risk of hemorrhage after AP
Majeed (2010)[105]	Retrospective journal study	AC 59 AP 0 No AT trtmt 118	No	Optimal resumption-time of AC: 10-30 weeks following intracranial hemorrhage
Yung (2012)[106]	Register-study	AC 91	No	No increased mortality in selected patients after restarting AC in hospital
Gathier (2013)[107]	Retrospective journal study	AC 12 AP 13 No AT trtmt 13	No	Inconclusive
Norrbotten (2014) (unpublished data)	Register-study	AC 64 AP 203 No AT trtmt 459	Only at baseline	No increased risk of hemorrhage after AP
Kuramatsu (2015)[108]	Multi-center cohort study	AC 172	Yes	Resumption of AC associated with fewer ischemic complications and no difference in hemorrhagic complications
Nielsen (2015)[109]	Nationwide cohort study	AC 621 AP 759	Yes	AC associated with reduction of ischemic stroke/all-cause mortality
Chao (2016)[110]	Nationwide cohort study	AC 1154 AP 3552 No AT trtmt 8211	Yes	AC may be beneficial in AF patients with CHA_2DS_2-VASc >= 6
Ottosen (2016)[111]	Nationwide cohort study	AC 160 AP 799 No AT trtmt 1959	No	AC associated with reduction of thromboembolic events/all-cause mortality

Temporal trends in Swedish stroke care

This thesis investigates aspects of stroke recurrence and secondary stroke prevention over an 18-year period in Sweden (1995–2012). Analyzing temporal trends in stroke recurrence risk, prognosis and management is difficult with no greater picture of recent developments. Figure 1 summarizes some of the important trends found in stroke management and treatment in Sweden 2001-2012. (Riksstroke data).

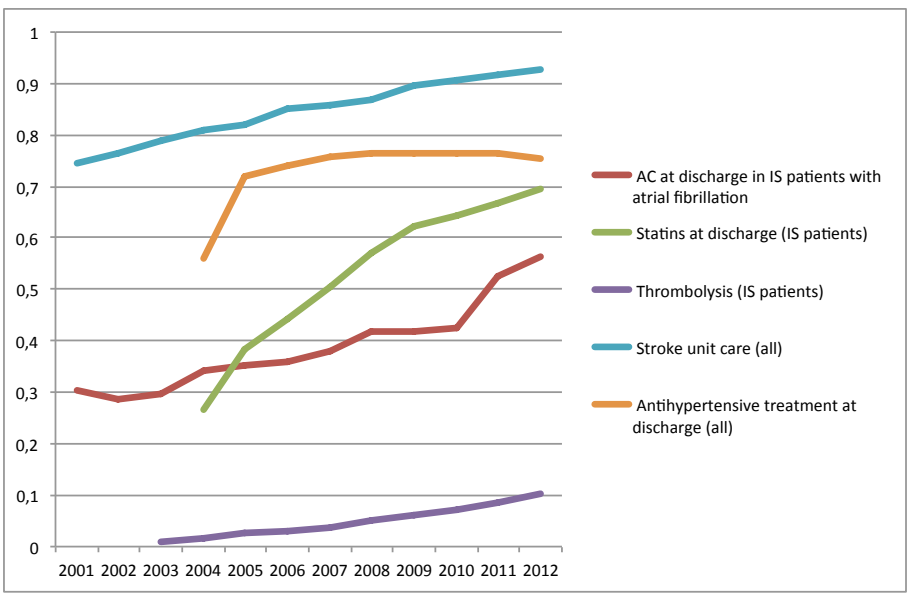


Figure 1. Trends in some aspects of stroke care in Sweden 2001-2012. The y-axis represents the proportion (1.0=100%) of patients registered in Riksstroke with first-ever stroke (IS, ICH or unspecified stroke) with regards to anticoagulation (AC) at discharge (only IS patients with AF), statins at discharge (IS patients), patients who were treated with thrombolysis (IS patients), patients treated in stroke units (all patients), and patients with antihypertensive treatment at discharge (all patients). (Riksstroke data).

Trends illustrated in figure 1 are related to research findings throughout the study period of which some of the most important in relation to this thesis are listed in table 3.[38, 51, 63, 64, 113-119] The identification of AF as an independent risk factor for IS[38], the introduction of, now widely used, risk classification scores[63, 64] and studies on oral anticoagulant treatment (AC) versus antiplatelets (AP) in terms of stroke prevention[116, 117] have most definitely contributed to the increasing use of ACs in IS survivors with AF. Publicly available between-hospital comparisons in the use of ACs after IS (Riksstroke) may also have contributed to this observation. Antihypertensive

treatment is effective in secondary prevention of both IS and ICH[120], and the PROGRESS trial demonstrated how the risk reduction is proportional to the degree of blood pressure lowering.[115] Lipid-lowering treatment (statins) is recommended as secondary prevention following IS (and TIA), associated with a reduction of stroke recurrence rates[118]. During the study period, a larger proportion of stroke patients also had access to stroke unit care, which has proven to reduce long-term death, dependency and institutionalization.[114] From a historical perspective, the prevention of recurrent stroke has been one of the major advances in stroke management over the last 40 years. In fact, in 1977 there was no proven secondary prevention strategy for stroke (AP following IS was not introduced until 1978).[13]

Table 3. Important studies with implications for the development of Swedish stroke care (excluding acute interventions) over the study period (1995–2012). (TE – thromboembolic)

Year	Study	Author	Main Findings
1989	AFASAK (Copenhagen Atrial Fibrillation, Aspirin and Anticoagulation)[113]	Petersen et al.	Incidence of TE complications and vascular mortality lower in AC group compared to AP and placebo
1991	The Framingham Study[38]	Wolf et al.	AF – an independent risk factor for IS
1997	Systematic review of RCTs of stroke unit (SU) care[114]	Stroke Unit Trialists' Collaboration	SU care associated with reduction in death, dependency and need for institutional care
2001	PROGRESS[115]	PROGRESS Collaborative Group	28% reduction in stroke risk in patients treated with ACE-i and diuretics compared to placebo
2001	Validation of clinical classification schemes for predicting stroke[63]	Gage et al.	$CHADS_2$-score for risk stratifying AF-patients
2002	Oral anticoagulants vs aspirin in non-valvular atrial fibrillation: an individual patient meta analysis[116]	Van Walraven	AC superior to AP to prevent stroke in chronic or paroxysmal AF
2004	AC (and AC vs. AP) for preventing stroke in patients with nonrheumatic atrial fibrillation[117]	Saxena et al.	AC superior to placebo and AP in preventing recurrent stroke in AF patients
2006	SPARCL[118]	Amarenco et al.	16% reduction in stroke risk with atorvastatin in IS patients without CHD in comparison with placebo
2007	Meta-analysis of AT to prevent stroke in patients with AF[51]	Hart et al.	AC reduces risk of IS in AF by around 60% and AP by around 20%
2009	AC for preventing recurrence following presumed non-cardioembolic IS or TIA[119]	Sandercock et al.	AC no better than AP or placebo in patients without cardioemboli, but increases risk of bleeding
2010	Refining clinical risk stratification for predicting stroke in AF[64]	Lip et al.	CHA_2DS_2-VASc introduced

Materials and methods

All studies within this thesis were observational studies based on register data. In paper I, stroke cases were retrieved from the population-based Northern Sweden Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Stroke Incidence Register. The study populations of papers II-IV were derived from a hospital-based register, the Swedish national quality register for stroke care (Riksstroke). To add information on comorbidity, medical treatment, cause and date of death and socioeconomic variables, data from the stroke registers were linked with other nationwide registers held by the National Board of Health and Welfare and Statistics Sweden. All registers used are described below and for an overview of linked registries in papers I–IV, please see table 4.

Table 4. Registers used in papers I-IV. (STA – Swedish Tax Agency (Folkbokf. – Folkbokföringen), NPR – National Patient Register, SPDR – Swedish Prescribed Drug Register, CDR – Cause of Death Register, LISA – Longitudinal Integration Database for Health Insurance and Labour Market Studies).

	Paper I	Paper II	Paper III	Paper IV
MONICA	x			
STA (Folkbokf.)	x			
Riksstroke		x	x	x
CDR		x	x	x
SPDR		x	x	
NPR		x	x	
LISA		x	x	x

The Northern Sweden MONICA Stroke Register

The two northernmost counties of Sweden, Norrbotten and Västerbotten, became a participating center in the international WHO MONICA project in 1985. The objective of the MONICA project was to continuously register the occurrence of MI and stroke to assess the relationship between temporal trends in mortality and morbidity rates and changes over time in known cardiovascular risk factors.[121] All data collecting has been standardized and validated to allow for analyzing these trends and for international comparisons.[122] In the Northern Sweden population-based MONICA stroke incidence registry (covering Norrbotten and Västerbotten), stroke events in the ages 25–74 years were adjudicated by trained nurses applying the WHO stroke criteria[122, 123], covering the years 1985–2009. Possible stroke cases were collected through screening of all hospital records, general

practitioners' reports and death certificates. Diagnoses of ICH and SAH were also based on specific neuroradiological findings or at autopsy. The register has been shown to capture 96% of all stroke events in the region.[124] As of 2008, the MONICA stroke incidence registry had registered and validated around 23000 stroke events in 18500 individuals. A diagnosis of unspecified stroke was assigned when no neuroimaging (or post-mortem examination in fatal cases) had been performed. Importantly, recurrent stroke events within 28 days from the initial stroke were not recorded in the register. Paper I is a population-based study based on data from MONICA stroke incidence registry, linked with population registries from the Swedish Tax Agency (STA) (Folkbokföringen) to obtain individual information on date of death or emigration.

Riksstroke – a national quality register

Today, there are more than 100 national quality registers in Sweden, collecting individual information on diagnosis, treatment and outcome that can be used to monitor and improve the quality of health care. Riksstroke, the Swedish national quality register for stroke care, was established in 1994, and since 1998 the register has covered all hospitals in Sweden admitting acute stroke patients (72 hospitals in 2014).[125] In recent years, the coverage of Riksstroke has been 90% when compared to the National Patient Register (NPR)[125] described below. Given the false positive diagnoses of acute stroke within the NPR (6% for first-time events and 12% for all stroke events)[126], the actual completeness of Riksstroke is probably well above 90%[125]. Riksstroke is the world´s longest-running national stroke quality register and includes data on the quality of care during the acute phase, rehabilitation and secondary prevention of stroke, as well as data on community support.[127] Eligible for registration are patients treated in hospital and diagnosed with IS (ICD-10: I63), ICH (ICD-10: I61), or unspecified acute cerebrovascular events (ICD-10: I64). As for the MONICA stroke register, recurrent events within the first 28 days from an acute stroke are not recorded as recurrent events. Figure 2 shows the numbers of registered patients from 1994 to 2015. Around 25% of all registrations each year over the last ten years have been recurrent events.

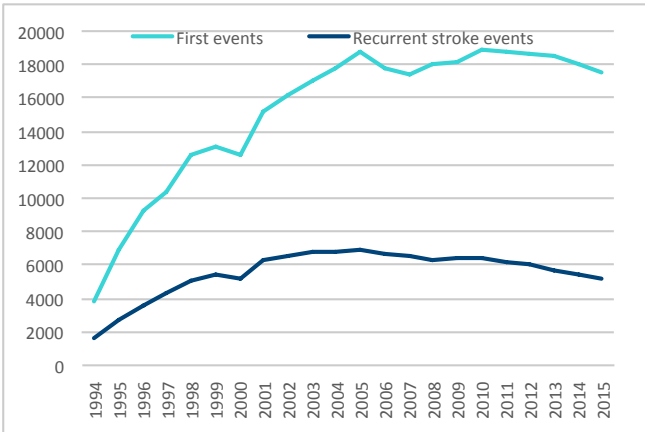


Figure 2. Numbers of registrations in Riksstroke from 1994 to 2015 divided into first-time stroke events and recurrent events. Reprinted with permission from the Riksstroke Organization.

Other national registers

The National Patient Register (NPR)

The Swedish National Inpatient Register (IPR) was founded in 1964, and by 1987 all counties had entered the register, which covers all somatic and psychiatric inpatient care in Sweden. The IPR is part of the National Patient Register (NPR) and all physicians, privately and publically funded are obliged to deliver data to the IPR. Since 2001, hospital-based outpatient visits have also been mandatory to report. Primary care is, however, still not included. In 2011, more than 99% of all somatic and psychiatric discharges were registered in the IPR.[128] The IPR includes data on 40.8 million discharges during the period 1988-2013, and it contains information on dates of admission and discharge, principal and additional diagnoses, age, sex and patients' unique personal identification numbers. The principal diagnosis is missing in 1% of the patients as is the personal identification number.[129] A validation study of the IPR suggests that the overall positive predictive value (PPV) of the diagnoses in the register is 85-95%.[128] As mentioned above, the validity of the IPR in the context of stroke has been assessed, with findings of false positive diagnoses of stroke in the IPR (6% for first-ever stroke and 12% for all-stroke events)[126]. Some other diagnoses that are relevant to this thesis are MI, AF and congestive heart failure. The PPV of MI was according to two different studies 98%[130] and 100%[131]. For AF, the PPV was 97%[132]. For heart failure PPV was 81.7%[133] and 88%[131] in two studies respectively. IPR sensitivity for MI was high (above 90%), but low for hyperlipidemia and hypertension.[134] Papers II and III used data from

the IPR to determine comorbidity. The coding of diagnoses in the IPR is according to the ICD. The current version, ICD-10, has been used in all counties reporting to the NRP since January 1, 1997, with the exception of Skåne where ICD-9 was in use throughout 1997 .[128]

The Swedish Prescribed Drug Register (SPDR)

Since July 1, 2005, the Swedish Dispensed Drug Register (SPDR) has collected data on all dispensed prescriptions from Swedish pharmacies, linked to a patient´s identity number.[135] Every year, more than 6 million inhabitants are registered in the SPDR, representing about two thirds of the Swedish population.[136] The numbers of prescribed purchases are around 100 million per year, and drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification.[137] An important limitation in relation to this thesis is that the SPDR does not carry any information on drugs used in inpatient care. (Papers II and III).

The Swedish Cause of Death Register (CDR)

Information on date of death during follow-up, and on principal and contributing causes of death was retrieved by individually linking Riksstroke data with the Cause of Death Register (CDR) that is also maintained by the National Board of Health and Welfare (papers II–IV).[5] Caution has been recommended when using the CDR in the context of stroke, because patients who are not hospitalized or are not treated in stroke units are less likely to be registered in the CDR as having died from stroke.[138] The validity of the NPR and CDR has recently been assessed and when information from the two registers are combined and refined, the PPV and sensitivity for acute stroke events are high. However, the precision is substantially higher when first-ever stroke events are recorded as compared to first- and recurrent stroke events.[126]

Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA)

To add information on socioeconomic variables such as educational level and income, Riksstroke data was linked to the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA by its Swedish acronym). The database is maintained by Statistics Sweden and intergrates data from the labour market, educational and social sectors.[139] Paper IV includes data obtained from LISA on highest attained level of education and the individuals' part of the family disposable income.

Variable definitions in Riksstroke

Some variables assessed in papers II-IV were common for all three papers and are therefore explained here:

a) Atrial fibrillation: Between 2001 and 2003, the coding for AF in Riksstroke was ”atrial fibrillation (including paroxysmal fibrillation and atrial flutter) at time of stroke”. From 2004 onwards, the definition was changed to also cover previously diagnosed AF and AF diagnosed during the hospital stay.
b) Hypertension was defined as on-going antihypertensive treatment at the time of stroke.
c) Diabetes mellitus included both earlier diagnosed diabetes and diagnosis during the hospital stay.
d) Independence in ADL (activities of daily living) was defined and registered when patients were able to manage toileting, dressing and walking unassisted prior to the stroke event.
e) Level of consciousness at admission, which is used as a proxy for stroke severity, was based on the Reaction Level Scale (RLS).[140] ”Fully conscious/alert” corresponds to RLS 1, ”drowsy” to RLS 2 and 3 and “unconscious” to RLS 4–8.

Further details on what information is collected are available at the Riksstroke website http://www.riks-stroke.org.

General statistical methods

More detailed descriptions of the statistical methods used in each paper are given in a separate section below. The general outline for the statistical analyses included the following;

1: Descriptive statistics (e.g. mean values, proportions)
2: Simple group comparisons (χ2-test (for categorical variables) or *t*-test (for continuous variables)).
3: Survival analysis (Kaplan-Meier estimates of survival, log rank tests, simple Cox proportional hazard regression)
4: Methods of controlling for confounding (stratified analyses, multivariable Cox proportional hazard regression models) (papers I–IV)
5: Competing risk analysis and analysis of time-dependent covariates (paper III).

For statistical analyses, SPSS versions 21.0 and 22.0 were used (papers I–IV). For statistical analyses in paper III, R[141] was additionally used. The level of significance was set to 0.05.

Survival analysis

In statistical terms, the time starting from a given point to the occurrence of a given event is called the *survival time* or more general *time to event* and the corresponding analysis the *time to event* or *survival analysis*[142] (in this thesis, e.g. time to stroke recurrence). *Censoring* is an important issue in survival analysis and occurs when information on survival time is incomplete. The most common form is called *right censoring*. One example of right censoring is when a patient does not experience the event of interest for the duration of the study.[143] Table 5 presents an overview of the survival analyses performed in papers I-IV.

Table 5. Overview of start time of follow-up, event-definitions and censored observations in papers I-IV.

Paper/Number of patients (N)	Time period investigated	Start time of follow-up	Event definition(s)	Censored observations
Paper I N = 6 700	January 1, 1995 - December 31, 2008	>28 days following IS or ICH	1) Stroke recurrence (IS, ICH, SAH or unspecified stroke) 2) Combined end-point of stroke recurrence or death	1) Death/ Emigration/ Turning 75 years of age 2) Emigration/ Turning 75 years of age 3) Study end
Paper II N = 14 045 AF: 2 777 No AF: 11 268	July 1, 2005 - December 31, 2012	Time of discharge from hospital after first ICH	1) Dispensed prescription of AC 2) Dispensed prescription of AP	1) Death/ Emigration 2) Study end
Paper III N = 2 619	July 1, 2005 - December 31, 2012	>28 days following ICH	1) Severe thrombotic event 2) Severe hemorrhagic event 3) Death from other causes	1) Emigration 2) Dual therapy 3) Study end
Paper IV N = 168 295	January 1, 2001 - December 31, 2012	>28 days following IS, ICH or unspecified stroke	Stroke recurrence (IS, ICH or unspecified stroke)	1) Death/ Emigration 2) Study end

Kaplan-Meier

The Kaplan-Meier (K-M) estimate[144] involves computing the probability of surviving a given length of time, and estimates are often presented as K-M survival curves. The *log rank test* is the most common method when it comes to assessing whether two K-M survival curves are significantly different, e.g. the curves for men and women. The *log rank test* calculates the χ^2 for each event time for each group and sums the results. The summed results for each group are added to derive the ultimate χ^2 to compare the full curves of each group.[145] Important assumptions are made in the K-M estimation. 1) We assume that patients who are censored, at any time, have the same survival prospects as those who are continued to be followed. 2) We also assume that the survival prospects are equal in those requited early and late in the study. 3) Finally, we assume that events happen at the specified times.[146]

Cox proportional hazard regression

Within this thesis, when the outcome of interest was time to event, the Cox proportional hazard (PH) model, described by Sir David Cox in 1972[147], was used. The Cox PH model is an example of a model of survival analysis and relates the time to event to one or more covariates (univariable or multivariable analysis respectively) that might (or might not) be associated with that quantity of time.

The Cox PH models the hazard function at time *t*, including one or more covariates. An important assumption made, is that of *proportional hazard*. This means that if a covariate, say diabetes, doubles the risk of stroke recurrence on day one, it also doubles the risk of recurrence on any other day. The proportional hazard assumption in the data for this thesis was verified by visual examination of the K-M survival curves in all studies using Cox PH regression.

In multivariable analysis, the choice of which variables to include was based on clinical relevance (for example known risk factors of stroke) and variables with certain levels of significance in univariable analysis. In paper I, smoking was omitted from further analysis due to a very large proportion of missing data. Outcome in Cox PH regression analyses were presented by hazard ratios (HRs) with corresponding 95% confidence intervals (CIs).

Competing risk analysis, time-dependent covariates and splines

Competing risk methods are commonly used when there is a need to deal with multiple potential outcome events.[148] The competing outcome variables (e.g. severe thrombotic events, severe hemorrhagic events and death from

other causes in paper III) all needed to be taken into account when trying to determine the observed risk/benefit of different treatment strategies.
When values of covariates (in this case AP and AC treatment) are presumed to vary with time, these covariates are said to be *time-dependent*. Most commonly, the relationship between covariates and time-to-event are modeled as linear (continuous covariates) or piecewise constant (categorical variables). When modeling treatment effects, we allowed a general form of the relationship to examine whether, and if so how, their effects were changing over time. Thus we used spline functions, which are well known for their usefulness in providing a smooth approximation to a covariate function, to model the relative risk in the Cox PH models[149].

Material and methods for papers I–IV

Paper I

Patients and variables
Predictors of stroke recurrence and stroke recurrence rates were analyzed in 6,700 patients between 25 and 74 years of age in Norrbotten and Västerbotten counties who survived the first 28 days following a first ever IS or ICH between 1995 and 2008. The start-time of follow-up was 28 days after the initial stroke. Prior to the start time of follow-up, there were 723 deaths yieldning 28-day case fatalities of 6.4% following IS and of 27.6% following ICH. In the analyses of recurrent stroke, recurrent IS and ICH as well as SAH and unspecified stroke events were included. Hypertension was defined as ongoing antihypertensive treatment at the first stroke event and data on previous MI included self-reported MIs and those documented in medical records. Previous TIA required documentation in the medical records. Diabetes included type 1, type 2, and unspecified forms of the disease prior to the first stroke as well as diabetes diagnosed during the hospital stay. The smoking variable rendered a high number of missing values (44%), why this variable was excluded from further analysis. To analyze time trends in recurrence rates, three cohorts were defined – index stroke occurring in 1995–1998 (n=2210), 1999–2003 (n=2384) and 2004–2008 (n=2106).

Statistical methods
Independent predictors of, and time to, stroke recurrence were analyzed by univariable Cox PH regression. To simultaneously analyze the effect of several predictors, multivariable Cox PH regression was used. Patients who died, moved out of the study region, turned 75 years of age or reached the study end date without experiencing a recurrent stroke were censored when assessing the risk of stroke recurrence only, and for the combined end-point

of stroke recurrence and death, patients were censored at moving out of the study region, turning 75 years of age or reaching the study end date.

Paper II

Patients and variables

Our analysis included 14,045 patients with a first-ever ICH registered in Riksstroke from July 1, 2005 through December 31, 2012, who survived hospital discharge and who had no previous record of ICH in the IPR from 1997 until registration in Riksstroke. Of these, 2,777 patients had concomitant AF and 11,268 did not. The diagnosis of AF was obtained from Riksstroke at time of ICH or was found in the IPR (ICD-10 I.48) from 1997 until ICH onset. Riksstroke data was linked with the SPDR to add information on the first dispensed prescription of AT treatment following hospital discharge. The ATC classification system was used for defining the subgroups of AT treatment: oral AC treatment (warfarin or NOACs, ATC-code B01AA, B01AE, B01AF) and AP therapy (ATC-code B01AC). Baseline data on antithrombotic treatment at time of ICH were obtained from Riksstroke, which contains information on current medication at the time of stroke. To investigate whether commonly used risk-stratifications scores for IS and bleeding in AF patients in whom AC treatment is considered (the CHA_2DS_2-VASc and HAS-BLED scores described earlier) were used, an estimation of each score was made for all patients with AF. A modified HAS-BLED score, similar to that of Friberg et al[45] was derived because data on international normalized ratio (INR) levels during anticoagulant therapy were not available. Moreover, in the concomitant medication variable of the HAS-BLED score, we were only able to include AP drugs, if any, at baseline. The alcohol index, based on a number of specific ICD diagnoses related to alcohol abuse[150], was used as a proxy for high alcohol consumption.

Statistical methods

To analyze the time to prescription of AT treatment (ACs and APs), HRs with 95% CIs were estimated using simple Cox PH regression for unadjusted analysis. All variables with p-values < 0.10 were included in subsequent multivariable Cox regression models. Patients were followed until prescriptions of AC and AP, until date of death, emigration or study end-date, whichever occurred first. Patients with prescriptions of both AC and AP were analyzed in both treatment groups. Because the CHA_2DS_2-VASc and HAS-BLED scores include information on other covariates, the risk scores were only assessed in the univariable model to avoid collinearity. Logistic regression, including year of ICH as a continuous covariate, was used to investigate temporal trends in concomitant AF, treatment at time of ICH, and treatment 1 year after discharge from hospital. Patients with and

without AF were analyzed separately, except in the analysis of resumption of therapy, where AF instead was included as a covariate.

Paper III

Patients and variables

A total of 2,777 patients (from paper II) with a first-ever ICH recorded in Riksstroke between July 1, 2005 and December 31, 2012 with a concomitant diagnosis of AF and surviving hospital discharge were included. AF was defined as having had a previous diagnosis of AF in the NPR from 1997 until time of ICH or having AF according to Riksstroke. AC and AP treatment at baseline was defined as having had a dispensed prescription 6 months prior to ICH or a recorded baseline treatment in Riksstroke. Three different outcome events were defined. *Severe thrombotic events* were defined as IS (fatal or non-fatal) or all causes of death directly or indirectly caused by a thrombotic event (MI or systemic arterial thromboembolism). *Severe hemorrhagic events* were defined as either a recurrent ICH or other fatal hemorrhagic events. Finally, *death from other causes* was defined as a third possible outcome. In order to calculate cumulative incidence functions (CIFs) for each outcome up to three years, we defined two different risk profiles with given sets of clinically important patient characteristics. The *low-risk profile* was 69 years of age, had no previous AT treatment, no additional risk factors (other than AF) and 14 days' hospital stay. In terms of CHA_2DS_2-VASc, 1 point if male and 2 points if female. The *high-risk profile* was 80 years of age and having spent 28 days in hospital. Further characteristics of this patient profile were previous IS, hypertension, diabetes and previous AC treatment at the time of ICH (by CHA_2DS_2-VASc; 6 points if male and 7 points if female). CIFs were calculated for men and women separately for both profiles. Additional *mid-risk profiles* (with CHA_2DS_2-VASc scores of 3 (4 if female)) were added to test the generalizability of our findings.

Statistical methods

The analysis of competing risk (several different endpoints) and different treatment strategies as time-dependent covariates required more sophisticated statistical modeling and analyses than those used in papers I-II and IV. In short, three different Cox PH models were created for each of the outcome events, one model for *severe thrombotic events*, one for *severe hemorrhagic events* and one model for *death from other causes*. This allowed us to adjust for differences in patient characteristics when computing the cause-specific hazards. To explore the relationship between starting times of AC and AP treatment and the competing risks of the three

outcome events, we focused our analyses on the estimation of cumulative incidence functions (CIFs). The CIF is the probability of observing an event before a specified time. CIFs were defined for thrombotic and hemorrhagic events separately and when summed these gave the CIF of the combined outcome "vascular death or non-fatal stroke". The time-dependent effects of the two antithrombotic treatment regimens were modeled though using splines, which allowed the effects of each treatment regime to vary with time. We decided to calculate the CIFs at three years after ICH for each outcome event in relation to treatment given at different time points since the ICH to illustrate the optimal timing of starting AT treatment.

Paper IV

Patients and variables

Patients with a first-ever IS, ICH, or unspecified stroke event registered in Riksstroke between 2001 and 2012, surviving for at least 28 days following stroke, and being independent in ADL prior to the ICH were included. A total of 168,295 patients fulfilled the inclusion criteria. The socioeconomic variables investigated were educational level, income level (retrieved from LISA) and cohabitation (Riksstroke). Highest attained educational level was grouped into primary school, secondary school and university. Income was measured using the individuals' portion of the family disposable income the year before the stroke, grouped into tertiles (low, middle, high). Cardiovascular risk factors assessed and included in the multivariable models were all retrieved from Riksstroke.

Statistical methods

The event variable of interest was that of stroke recurrence, implying that patients were censored at death, emigration or at study end, whichever came first. K-M survival curves were used to estimate cumulative rates of stroke recurrence, and independent predictors of stroke recurrence were assessed by univariable Cox PH regression. To investigate the impact of confounding, both a basic Cox PH model (adjusting for age groups, sex, hospital and time-period of first stroke) and full Cox PH models (additionally adjusting for AF, hypertension, smoking, diabetes, level of consciousness, type of first stroke and stroke unit care) were analyzed for significant predictors of stroke recurrence. We added time-period-by-SES, and sex-by-SES interaction terms to the basic model to investigate whether the effects of SES changed over time or differed between men and women. To illustrate temporal trends in the associations between recurrent stroke and education and income, two cohorts were created (2001–2008 and 2009–2012), and education was grouped into primary/secondary school vs. university and income into low/middle income vs the highest tertile.

Ethical considerations

The unique personal identification numbers used in Sweden makes it possible to link data in different nationwide registers. To preserve patient integrity, personal identification numbers were removed immediately from the analysis data after linkage.

All individuals registered in MONICA were informed that they were registered and that they had the right to withdraw from the register at any time (opt-out consent).

All patients are informed through Riksstroke that they are registered in the nationwide register aiming to improve and enhance an equal stroke care in all hospitals in Sweden and that data may be used for research purposes. Every patient is informed that they have the right to withdraw from the registry (opt-out consent), but so far only a few per thousand have decided to do so.

The work in paper I was approved by the Ethical Review Board, Umeå, Sweden (Dnr 07-085M), dated 2007-06-05.

Approval for the work in papers II and III was obtained from the Ethical Review Board, Umeå, Sweden (Dnr 2014-76-32M), as an extension from the EqualStroke project (Dnr 2012-321-31M), dated 2014-02-24.

The work in paper IV was approved according to Dnr 2012-321-31M, dated 2012-10-02.

Results

Baseline characteristics and simple group comparisons of the study populations

The main characteristics of the patients included in papers I–IV are presented in table 6. The main difference between the MONICA (paper I) and Riksstroke study populations (paper II–IV) is that of the age distribution. MONICA only registered patients between 25–74 years of age while Riksstroke covered all ages from 18 years and older.

Table 6. Baseline characteristics of study populations paper I-IV.

	Paper I	Paper II	Paper III	Paper IV
N(%)	6700 (100)	14045 (100)	2619 (100)	168295 (100)
Index stroke subtype	IS/ICH	ICH	ICH	IS/ICH/ unspecified stroke
Mean age	63.9	71.5	78.0	73.6
Female sex	2608(38.9)	6121(43.6)	1065(40.7)	81080(48.2)
Atrial Fibrillation	1004(15.0)	2777(19.8)	2619(100)	38698(23.6)
Hypertension	3443(51.4)	10020(71.3)	2180(83.2)	86356(51.3)
Diabetes	1322(19.7)	2318(16.5)	605(23.1)	30651(18.2)
Previous IS	0(0)	2185(15.6)	640(24.4)	0(0)
Previous myocardial infarction/ischemic heart disease	703(10.3)	2278(16.2)	713(27.2)	-
Valvular disease	-	379(2.7)	213(8.1)	-
Educational level				
Primary school	-	6190(44.1)	1309(50)	83451(49.6)
Secondary school	-	5111(36.4)	900(13.7)	56358(33.5)
University	-	2422(17.2)	360(13.7)	23691(14.1)
Antithrombotic Treatment at baseline	-			-
Anticoagulants	-	1454(10.4)	1239(47.3)	-
Antiplatelets	-	4018(28.6)	1175(44.9)	-

Patients with ICH (n=815), compared to those with IS (n=5885) were younger and were less prone to have traditional cardiovascular risk factors, such as hypertension, previous MI, AF and diabetes (paper I). Paper II enabled the comparison between ICH survivors with and without AF, and showed that AF patients were significantly older, more often female and carried a larger burden of comorbidity such as diabetes, previous IS, venous thromboembolism (VTE), ischemic heart disease, hypertension, valvular disease, renal and thyroid disease, heart failure and dementia. Comparing baseline characteristics in AF patients between those prescribed AC within 8 weeks of hospital discharge to those who received no antithrombotic treatment showed that patients who received ACs were less likely to be dependent in p-ADL prior to ICH but more likely to suffer from diabetes, VTE, hyperlipidemia and valvular disease (paper III).

Stroke recurrence rates and predictors (paper I, IV)

Paper I: The cumulative risk of stroke recurrence in the MONICA cohort was 6% at 1 year after the initial stroke event and the 5- and 10-year cumulative risk of stroke recurrence was 16% and 25% respectively. The corresponding figures for a combined endpoint of stroke recurrence or death from any cause were 10%, 28% and 45% at 1, 5 and 10 years after the initial stroke event. The risk of stroke recurrence was less prevalent in the most recent cohort (2004–2008) (HR: 0.64, 95% CI: 0.52– 0.78) compared to the first cohort (1995–1998), as shown in figure 3.

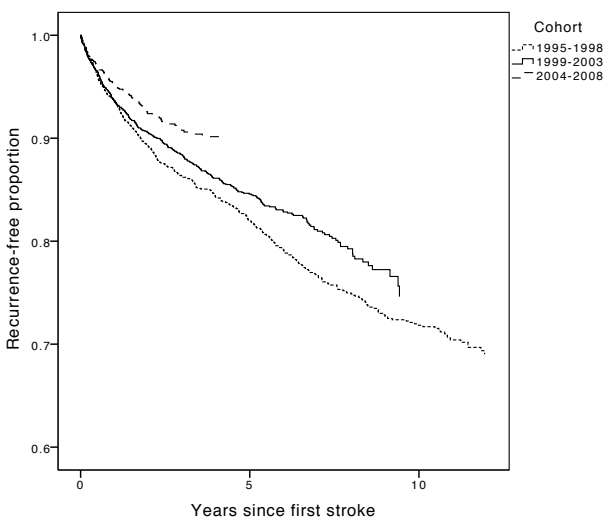


Figure 3. Kaplan-Meier survival curves of time to stroke recurrence, for the three cohorts.

Comparing baseline characteristics between the different cohorts, we found that a history of MI was less prevalent in the most recent cohort (p<0.001), whereas other potential risk factors for stroke recurrence did not vary significantly among the three cohorts. Significant predictors of *recurrent stroke* in multivariable analysis were diabetes mellitus, HR(95%CI): 1.34(1.15-1.57) and advanced age. Hypertension did not reach statistical significance (HR: 1.15, 95% CI: 1.00–1.32).
For the combined end-point of *recurrent stroke and death* additional cardiovascular risk factors were significant predictors, including hypertension, AF, previous TIA, history of MI and male sex.

Paper IV: K-M estimates of the cumulative risk of stroke recurrence were 5.7% at 1 year, 17.1% at 5 years, and 27.1% at 10 years after the initial stroke event. Lower levels of income and education were associated with an increased risk of recurrent stroke, as was single habitation. Also in paper IV, we found a temporal trend of decreasing risk of recurrence (HR: 0.828, 95% CI: 0.777-0.883) for the 2011–2012 cohort compared to the first cohort of 2001-2002.

There were no significant interactions between the time period of first stroke and educational level (p=0.467) or income group (p=0.659), implying that the disparities in risk of stroke recurrence between the highest educational and income groups relative to those in the lower socioeconomic groups remained of similar magnitude throughout the 2001–2012 study period (figure 4).

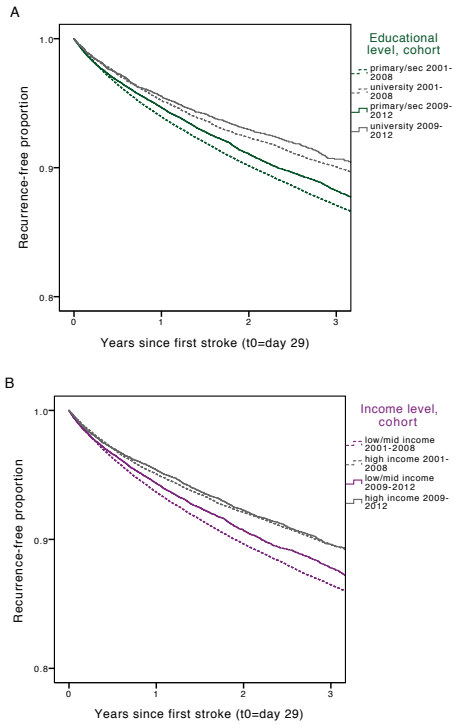


Figure 4. Kaplan-Meier survival curves of time to stroke recurrence up to 3 years following first-ever stroke, separate lines for cohort (2001-2008, 2009-2012), educational level groups (A) and income level groups (B). Both analyses include all ages and only include patients with complete data, n = 163,500 in (A) and n = 168,031 in (B).

A separate interaction analysis did not find any difference in the inverse effects of lower SES between men and women (educational level, *p*-value for interaction = 0.532, income: *p*-value for interaction = 0.322). Apart from the SES variables, other significant predictors of stroke recurrence in the full Cox PH regression models were age, male sex, diabetes, hypertension, AF and smoking (data not shown).

Recurrent stroke subtypes (papers I and IV)

Of all recurrent events after ICH, 62% were ischemic in the MONICA population (paper I). Repeating the analysis in paper IV, the corresponding figure was 57% (figure 5). During follow-up we observed 928 recurrent stroke events in paper I, and 22,735 recurrent events (following IS or ICH) in paper IV.

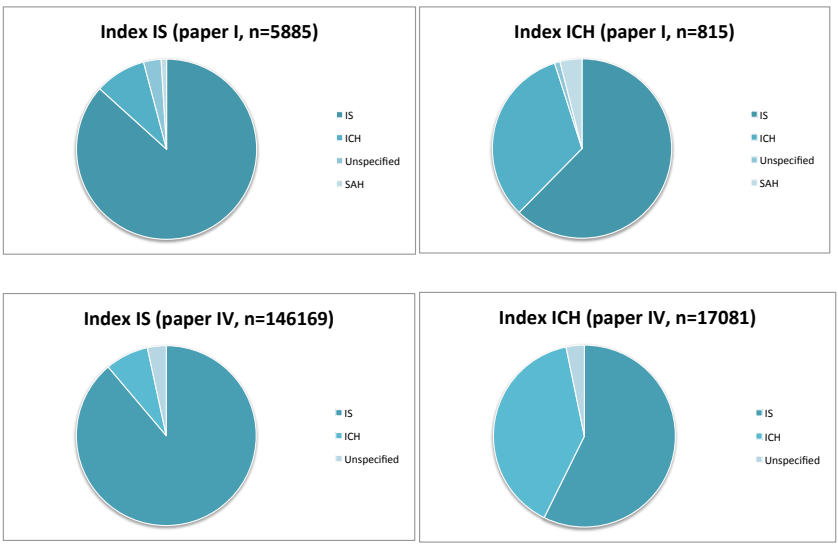


Figure 5. The distribution of subtypes of recurrent events following IS and ICH in papers I and IV.

Antithrombotic treatment following ICH (paper II)

Of 14,045 patients with ICH, 10.4% were on ACs, 28.6% were on AP drugs and 0.9% were on both drugs at time of ICH (paper II). Independent predictors of resuming anticoagulant treatment were younger age, lower stroke severity and valvular disease. Previous ischemic stroke did not show any association with restarting anticoagulants and patients with concurrent AF were less likely to restart AC than those without AF (HR: 0.72, 95% CI: 0.55–0.95).

One year following hospital discharge, 43.6% of patients with ICH and AF (n = 2,777) had had a dispensed prescription of APs and 11.1% had received ACs (figure 6). The corresponding figures in patients without AF (n=11,268) were 17.5% with prescribed AP, and 2% had received AC treatment within one year from discharge.

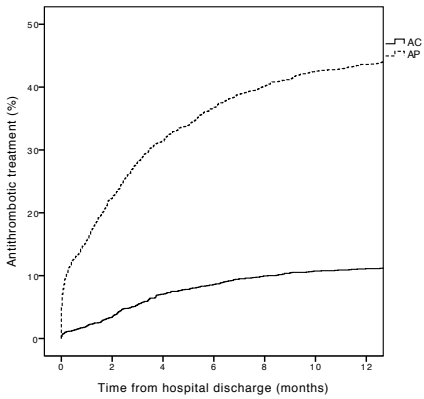


Figure 6. Kaplan-Meier curves of time to dispensed prescriptions of anticoagulant (AC) and antiplatelet (AP) treatment in patients with atrial fibrillation (AF) following intracerebral hemorrhage (ICH)

Factors associated with dispensed prescriptions of AC in AF patients were younger age, previous IS, less severe ICH, valvular disease and AC at baseline (figure 7).

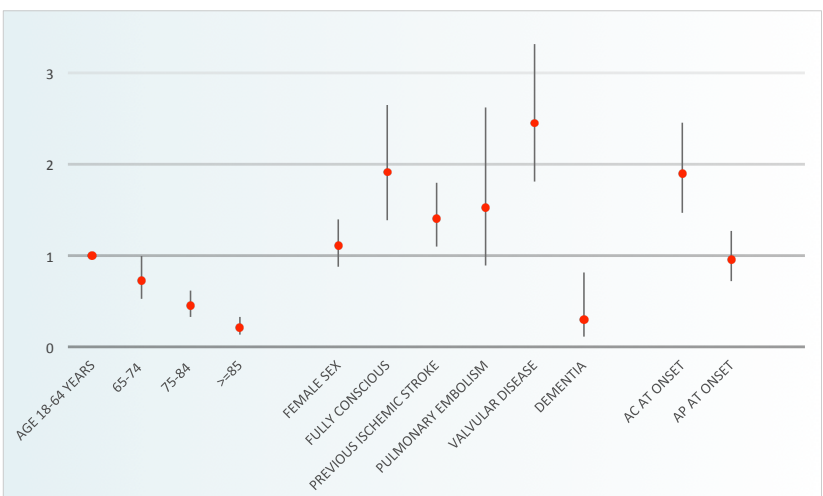


Figure 7. Predictors of prescriptions of anticoagulants (AC) and antiplatelets (AP) in patients with atrial fibrillation (AF) following intracerebral hemorrhage (ICH). Hazard ratios with 95% confidence intervals from multivariable Cox regression.

Significant predictors for AP in AF patients were less severe ICH, previous IS, hypertension, and both AC and AP at the time of ICH.

Do risk stratification scores guide the decision to treat?

There was a positive correlation between high CHA_2DS_2-VASc and HAS-BLED scores in ICH-survivors with AF (r_s=0.590, p<0.001). The median CHA_2DS_2-VASc score was 4 and only 4.2% of the AF population scored below 2 points. A total of 13% of the patients presented with a HAS-BLED score of less than 3 points. High CHA_2DS_2-VASc scores did not seem to correlate with an increased probability of receiving AC following ICH, rather the inverse relationship was observed (figure 8).

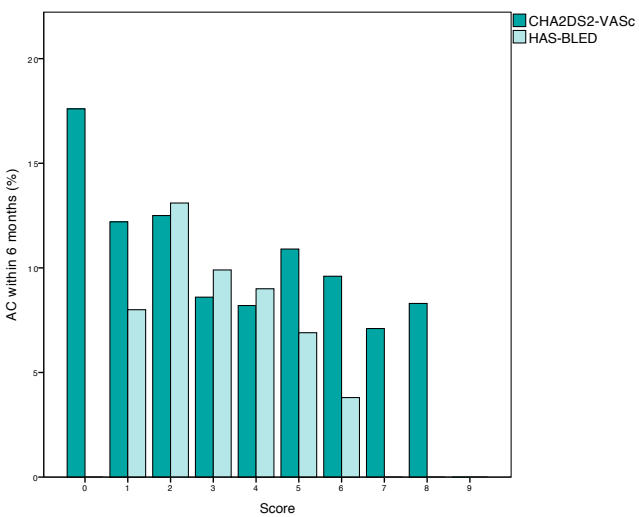


Figure 8. Percentage of ICH survivors with AF with AC treatment within 6 months, in different CHA_2DS_2-VASc- and HAS-BLED scores.

Temporal trends in antithrombotic treatment (paper II)

We observed an increasing use of AC treatment at the time of ICH (8.1% in 2006 compared with 14.6% in 2012, $p<0.001$ assuming a linear trend) and there was also a trend towards a larger proportion of ICH survivors with concomitant AF (17.7% in 2006 compared with 22% in 2012, $p<0.001$ assuming a linear trend).

In patients with AF, there were large regional variations in clinical practice, regarding subsequent use of AC. We also found an overall increasing use of AC one year after discharge in AF patients (8.3% in 2006 versus 17.2% in 2011, $p<0.001$ assuming a linear trend).

Optimal timing of treatment (paper III)

During follow-up, we observed 379 severe thrombotic events in 2,619 ICH-survivors with AF, of which 302 (79.7%) were IS events. Of 115 severe hemorrhagic events during follow-up 96 (83.5%) were recurrent ICHs. The 28-day case fatality following IS was 17.5% compared to 37.5% after recurrent ICH events. The 3-year empirical cumulative incidence was 14.5% for of thrombotic events and 4.4% for hemorrhagic events.

Before presenting the main findings of paper III, it is important to keep in mind the characteristics of the different patient profiles that were used in our statistical analyses to illustrate the effects of AT treatment in AF patients following ICH (see table 7).

Table 7. Patient risk-profiles illustrated in paper III regarding the estimated 3-year cumulative incidence of severe subsequent events following ICH in relation to the timing of antithrombotic treatment (AC or AP).

Patient profiles	Low-risk	High-risk	Mid-risk 1	Mid-risk 2
Age	69	80	78	78
Duration of hospital stay (days)	14	28	19	19
Hypertension	No	Yes	Yes	No
Diabetes	No	Yes	No	Yes
Previous IS	No	Yes	No	No
AC at time of ICH	No	Yes	Yes	Yes
Corresponding CHA_2DS_2-VASc score male(female)	1(2)	6(7)	3(4)	3(4)

Figure 8 presents the main findings of paper III, illustrating the optimal timing of treatment and the effects of different treatment strategies (AP or AC vs. no treatment) on the estimated event rates of thrombotic and hemorrhagic events and on the combined endpoints respectively. CIFs at 3 years after the onset of ICH vs. start time of two treatments (AC=green line, AP = red line) and no treatment (blue line) for both a low-risk and a high-risk female/male profile (A = female profiles, B = male profiles) are presented. The 3-year event specific CIFs of thrombotic and hemorrhagic events sum to the combined-event CIFs (vascular death or stroke) in the bottom row. The shaded areas and thick colored lines represent time periods during which treatment initiation of AC (green) and AP (red) is significantly different from no treatment at the 5% level.

In high-risk women, the total risk of vascular death or stroke recurrence within 3 years was 17.0% when AC treatment was initiated 8 weeks after ICH and 28.6% with no antithrombotic treatment (95% CI for difference: 1.4% to 21.8%). For high-risk men, the corresponding risks were 14.3% vs. 23.6% (95% CI for difference: 0.4% to 18.2%).

The interpretation of figure 8 is that AC treatment within the start time interval of 4–16 weeks following ICH significantly reduces the 3-year risk of subsequent thrombotic events both in high-risk and low-risk patients compared to no treatment. There might be an increased risk of bleeding if AC treatment is initiated before 7 weeks (however not statistically significant), and the combined endpoint suggests that the optimal timing for AC in patients with AF is around 7–8 weeks following ICH to minimize risk. In confirmatory analysis of the combined endpoint of all three outcome events (thrombotic, hemorrhagic and death from other causes) the beneficial effects of AC treatment were seen in both high- and low-risk patients within the same time frame (data not shown). For additional mid-risk patient profiles, see figure 9.

AP treatment seems to have no protective effect in any of these patient profiles, on the contrary, it was associated with a less favorable outcome for most of the times for starting treatment.

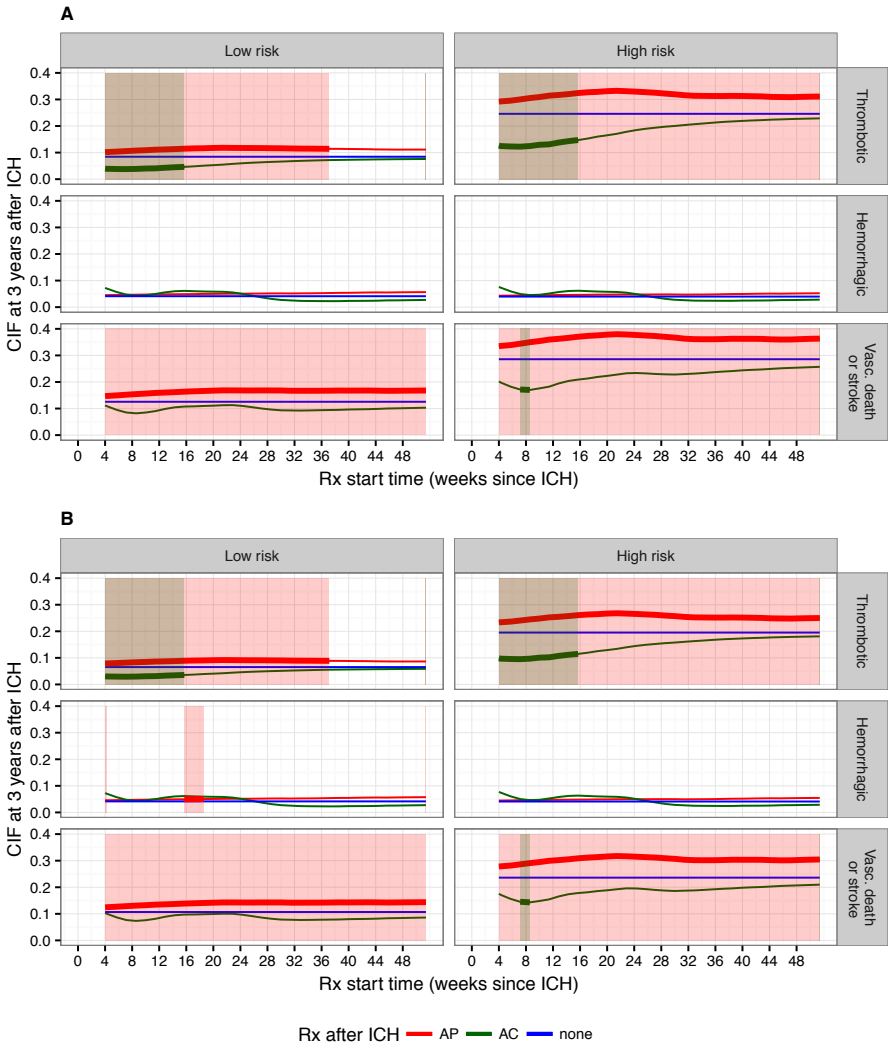


Figure 8. Cumulative incidence functions at 3 years following ICH in AF patients. Panel A: Female profiles, panel B: Male profiles. A high-risk patient was defined as being 80 years of age, having spent 28 days in hospital, having had a previous IS, suffering from hypertension, diabetes and being on AC treatment at the time of ICH. The low-risk patient was defined as being 69 years of age, having spent 14 days in hospital, having had no previous AT treatment and no additional risk factors for ischemic disease apart from AF.

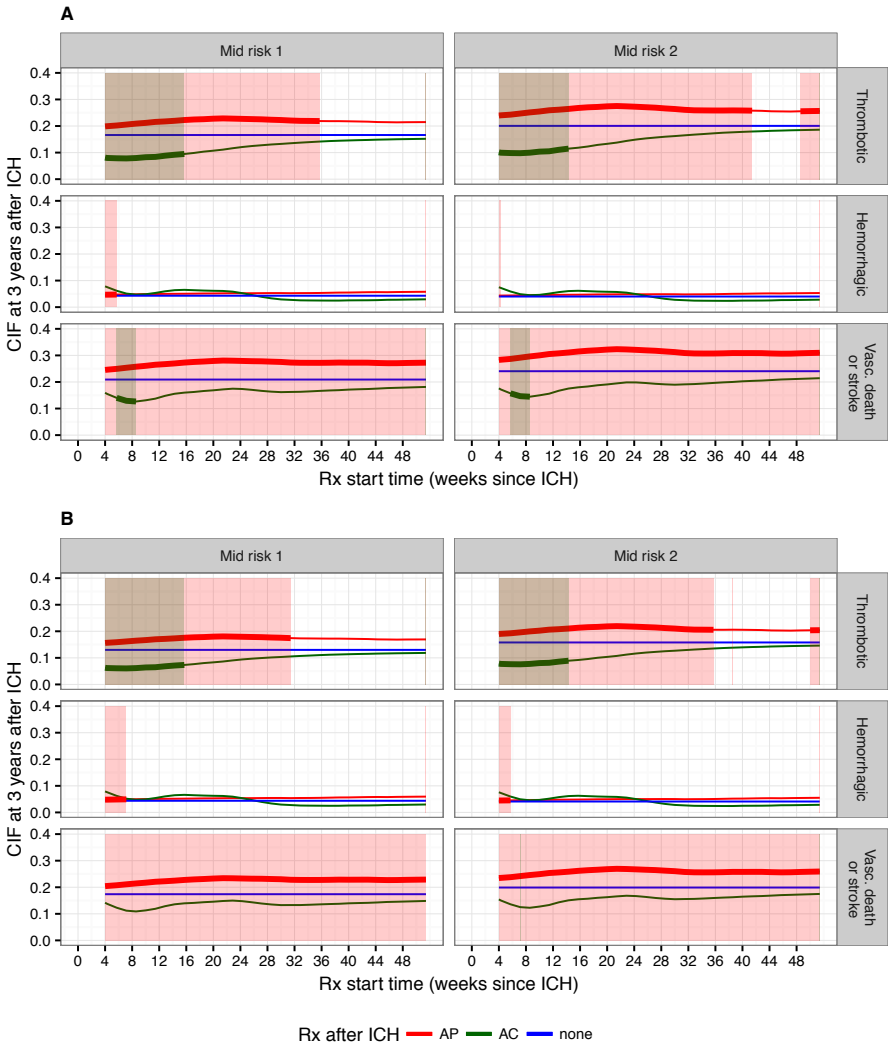


Figure 9. Cumulative incidence functions at 3 years following ICH in AF patients. Panel A: Female profiles, panel B: Male profiles. A "mid risk 1" patient was defined as being 78 years of age, having spent 19 days in hospital, having had previous hypertension and being on AC treatment at time of ICH. The "mid risk 2" patient was 78 years of age, spent 19 days in hospital, having had previous diabetes and being on AC treatment at the time of ICH.

Discussion

Methodological Considerations

Selection bias in population-based and hospital-based registers

The strength of the population-based design of the MONICA register is the very high degree of case ascertainment, stroke diagnoses within the register were based on uniform WHO diagnostic criteria over the study period[122]. The register is well-validated, and standardized case-finding procedures captured around 96% of *all stroke events* in Norrbotten and Västerbotten[124]. This makes it extremely unlikely that selection bias would affect the results of our MONICA study.

The strengths of a nationwide health quality register, such as Riksstroke, are the contribution of substantially larger study materials and the fact that inclusion criteria are not restricted by age. The coverage of Riksstroke is high, estimated at well above 90% of *all stroke patients treated in Swedish hospitals*, but the hospital-based design of Riksstroke may result in *selection bias at inclusion*. Not all stroke patients are admitted to hospital and a hospital-based stroke register can therefore not fully ascertain the incidence of first-ever or recurrent stroke events within a population.[151, 152] Previous studies have reported that 84%–92% of Swedish stroke patients are treated in hospital during the acute phase.[152, 153] Predicting which patients who are more likely to present to hospital is impossible, because patients with very mild or very severe strokes might not present to hospital for various reasons.[154] Previous research has demonstrated that patients in institutionalized care and those with less severe stroke events are less likely to be admitted to hospital[153]. Furthermore, patients treated in stroke units are more likely to be registered in Riksstroke compared to patients treated in other wards and fatal in-hospital strokes are less likely to be registered[155].

Since 2010, hospital admissions for acute stroke in Sweden have decreased by 8%[156] and there has been a 10% decrease in the number of hospital beds for acute stroke care within the same time period[157]. In the light of our results from the MONICA study, and considering reports on reduced stroke incidence rates in high-income countries[10, 158], the reduced admissions for acute stroke in Riksstroke is most likely a real finding, reflecting a sharp, favorable secular trend of lower stroke incidence rates in Sweden (Stegmayr et al.[159] and unpublished data, Northern Sweden MONICA project).

However, in absolute numbers both studies of recurrent events (papers I and IV) were most certainly underestimating the true rates, not because of selection bias, but due to the definition of stroke recurrence. The definition of recurrent stroke affects the reported recurrence rates,[160] and recurrent events within the first 28 days were not recorded in the MONICA study nor are they recorded in Riksstroke.

Selection bias is unlikely to have affected the results of socioeconomic predictors of stroke recurrence, it is highly unlikely that patients with lower SES would be more likely to present to hospital with a recurrent stroke than those with higher SES.

Confounding

A major challenge in observational, non-randomized studies is that of controlling for *confounding* factors – extraneous factors that not only affect outcome, but also the investigated exposure. There are a number of methods used to adjust for confounding, e.g. stratification and multivariable regression, but these methods may only control for known or measured variables. In all of our studies, there is a risk of *residual confounding*.

One of the most important considerations for paper II and III has also been that of the unavoidable risk of *confounding by indication,* a special type of confounding that occurs in observational pharmacoepidemiological studies. The use of antithrombotic drugs in papers II and III was not random, and the possibility of unmeasured selection factors cannot be overlooked in investigating predictors of treatment (paper II) and outcome (paper III). For example, we had no information on ICH location, hematoma expansion or ICH volume, all of which are factors that most certainly influence clinicians' decision to treat. We also lacked information on patients' preferences.

Information bias and missing data

Information bias arises from measurement errors, including misclassifications of both levels of exposure and of the outcome variable itself. The content validity of the Riksstroke acute form is high, and so is inter-hospital realibility.[125] MONICA is well validated[123, 124] and all data collecting has been standardized.[122] However, all sources of bias due to possible recording errors in MONICA and Riksstroke cannot be eliminated. These errors should be regarded as non-differential misclassifications and thus unlikely to have influenced our overall results. The definition of the AF variable in Riksstroke was changed in 2004. Hence, this cannot have affected the results of papers II and III, including patients from July 1, 2005.

An example of differential misclassification is that of elderly stroke patients missing data on educational level in paper IV. Here, we chose to conduct a sensitivity analysis in patients <75 years of age, returning very similar results as for the total study population. Missing data were generally analyzed as a separate category in our studies when categories had more than 2% missing data.

Violation of statistical assumptions, collinearity and overfitting

Apart from sources of bias mentioned above such as *selection bias*, *confounding* and *information bias*, new sources or errors and bias may emerge upon analysis such as those due to violations of assumptions, over-adjustment and inappropriate modeling[161]. Returning to the Cox regression, which is central to all our studies, major deviations from the PH assumption were identified by assessing K-M curves. The shape of K-M curves also suggests time points after which results should be interpreted with caution, as illustrated by more horizontal steps, as a result of the smaller numbers of patients at risk.

Collinearity arises when variables in a multivariable regression model are highly correlated. To evaluate the effect of collinearity we used both univariable and multivariable models. To reduce the effects of collinearity we did not add the CHA_2DS_2-VASc and HAS-BLED scores to the multivariable analyses of paper II and III, because these scores include information on other covariates (e.g. age and hypertension). In paper IV we did not include education and income in the same model in the main analysis. However, a sensitivity analysis including both education and income in the multivariable analysis of time to stroke recurrence was conducted due to previous research findings showing a relatively low correlation between these SES variables[162]. The analysis returned very similar results as when they were analyzed separately.

Overfitting of statistical models occurs when random errors are described instead of the underlying relationship. For paper III, in modeling the effect of treatment options for different starting times, we assumed a linear relationship of the effects of treatment beyond a certain time point, and this choice was motivated by the data (where we had fewer observations) in order to reduce this risk.

To test the *robustness of the statistical model* in paper III, a sensitivity analysis for various additional patient profiles was conducted, adding one risk factor at a time to the model of CIFs at 3 years. The resulting optimal

start times were all found to be within the range of 7–8 weeks after the onset of ICH.

Generalizability of the results

Guidelines for helping clinicians and patients choose between treatment options should preferably be based on sound clinical evidence derived from well-conducted studies and prospective RCTs.[163] Thus one cannot thoroughly discuss the findings of paper III without further reflecting on the differences between observational studies and RCTs. RCTs provide information on the efficacy of agents tested, in controlled clinical trial environments, often with highly motivated patients, usually with high compliance. While RCTs might answer the question as to whether a treatment regime works under such "ideal" circumstances (efficacy), real-world data, obtained through observational studies, may help answering the question of whether the treatment regime works under "usual" circumstances (efficiency).

Trial generalizability (external validity) is a recognized problem in RCTs. Participants in RCTs might differ considerably from the target population in which findings are later used, and trial inclusion criteria can contribute to this lack of generalizability.[164] Additionally, observational studies are more suitable for detecting late or adverse effects of treatments.[165] Observational studies also have generalizability issues, perhaps confounding by indication (discussed above) being the most relevant. Furthermore, the results of paper III need to be interpreted with an intention-to-treat-approach considering the lack of adherence data.

Another concern regarding the generalizability of the results in paper III is that of the choice of patient risk profiles. Many patients were in between those of our chosen "high-risk" and "low-risk" profiles. However, confirmatory analyses of several additional risk profiles did not change the overall results of the significantly reduced risk of thrombotic events with no excess risk of hemorrhage with AC or the optimal time window of AC initiation, in ICH survivors with AF.

General discussion of main findings

Favorable trends in stroke recurrence

The explanation for the favorable, declining rates of stroke recurrence in Sweden over the study period is most likely multifactorial and our findings of decreasing rates of recurrence are well in line with previous studies from high-income countries[75, 166]. There have been major improvements in

cardiovascular risk factor management (such as less smoking and lowered lipid and blood pressure levels) over the past two decades in the population of Northern Sweden.[167] In first-ever stroke patients aged 25–74 we found that the prevalence of previous MI has decreased in line with other findings of substantial reduction of the incidence of MI in Sweden.[168, 169] As for secondary prevention measures, a larger proportion of IS patients get the recommended treatment following stroke. Thus, the use of statins[71] and APs[166] in IS has increased and more IS patients with AF receive AC treatment[170]. A larger proportion of patients have benefitted from stroke unit care during the acute phase [70], probably associated with more structured initiation of secondary prevention measures.

Regardless of the overall promising trend of decreasing risk of recurrence, stroke recurrence is still affecting around 1 out of 6 patients within 5 years and almost 30% either died or suffered a second stroke within 5 years from the first stroke, in the 25–74 year age group. Two of the most consistently published risk factors for stroke recurrence – age and diabetes mellitus – were also found in the MONICA study. Our study investigating the effects of SES on risk of recurrence is by far the largest study on this topic, and we were able to adjust for traditional cardiovascular risk factors. Both low income and a low educational level were independent predictors of stroke recurrence. Contrary to previous studies[87, 88] we found that the increased risk of recurrence in low SES groups is similar in men and women, and we also conclude that this relationship has remained over time.

There is strong evidence for inverse relationships between SES and stroke incidence and mortality[171-173] and our study now adds the association with increased risk of recurrent stroke. Contributing explanatory factors of our findings could be the previously reported social stratification in secondary prevention[71, 174] and less access to stroke unit care in lower socioeconomic groups during the years assessed.[70] Regardless of the underlying causes, more studies on how to better implement secondary measures in targeted socially underprivileged risk groups seem warranted.

Antithrombotic treatment following ICH: ongoing changes in clinical practice and a positive effect of AC in AF patients

Of all Swedish ICH patients, around 40% were treated with antithrombotic agents at time of ICH, a level well in line with reports from other European countries[175, 176]. There were large regional variations in initiating AC treatment in ICH survivors, also consistent with previous findings[175], most likely reflecting the lack of consensus. The clinical dilemma has sometimes been perceived as being stuck between a rock and a hard place. Other

aphorisms on the topic of anticoagulation following ICH have been many; "How wide is the strait between Scylla and Charybdis"[177], "Primum non nocere"[178], "A risky decision with no recipe"[179]. Despite the lack of firm recommendations, there has been a change in clinical practice over the years studied, and a larger proportion of patients with AF receive AC treatment following ICH in more recent years. In a majority of patients who receive treatment, antithrombotic agents are initiated within the first 6 months of ICH. Still, many patients with compelling indications for treatment are not prescribed these agents. The CHA_2DS_2-VASc score does not seem to guide clinicians in the decision. On the contrary, a smaller proportion of patients with AF and high risk scores receive treatment within 6 months compared to those with low scores. Instead (apart from previous IS) other factors *not* incorporated in the score; such as younger age, AC treatment at baseline, valvular disease and less severe ICH predicted subsequent AC treatment among ICH survivors with AF.

Our study on outcome and optimal timing of AC following ICH in AF patients has important limitations (some of which are discussed in the above methodological section). However, our study supports that clinicians have made the right decision to treat, when they chose to do so, over the study period. The findings of reduced risk of severe thrombotic events and the combined endpoint of vascular death and non-fatal stroke is in line with emerging evidence of the overall beneficial effect of AC even after severe hemorrhages[109, 111, 180]. Still, none of these studies have identified the optimal time window for anticoagulant treatment and previous studies on optimal timing have been of relatively small sample size[103, 105]. However, in terms of overall net-benefit of treatment, our results are in line with those of Majeed et al.[105], suggesting that very early initiation of treatment might increase the risk of bleeding (but the risk was not statistically significant in our results). Our findings, with a larger study population have also been able to narrow the optimal timing window (from 10-30 weeks in the Majeed et al. study[105]) to 7–8 weeks following ICH. This may be an important message, especially that the opportunity of early effective secondary prevention should not be missed.

In an era of increasing use of highly potent drugs that are known for their adverse effects (i.e. ACs and hemorrhagic complications), we will most certainly see more complications, if such a trend continues. There are ongoing RCTs to try and help answer the question of whether and how to treat ICH survivors with indication for antithrombotic drugs. APACHE-AF[181] in the Netherlands (Apixaban versus Antiplatelet Drugs or no antithrombotic drugs after anticoagulation-associated intraCerebral HaEmorrhage in Patients With Atrial Fibrillation) and RESTART (REstart or

STop Antithrombotics Randomised Trial) in the UK[182] are examples of ongoing RCTs addressing the question of AT treatment following ICH. As an alternative to AC treatment, there is also a RCT evaluating surgical occlusion of the left atrial appendage in patients with AF following ICH, STROKECLOSE[183].

It is, however, unlikely that any of the ongoing RCTs will have sufficient statistical power to determine the optimal time span for treatment. For example, in the APACHE-AF study (aiming to include 100 patients), treatment with any of the antithrombotic drugs can commence at any time between 7 and 90 days following ICH, at the discretion of the physician[181]. While awaiting results from RCTs, observational studies constitute the best available scientific evidence.

Conclusions

There has been a substantial decrease of stroke recurrence risk over the last two decades in Sweden. Still, around 1 in 6 stroke patients have a second stroke within five years from the first stroke event, in spite of favorable trends in cardiovascular risk factors and major advances in secondary preventative measures.

Our findings confirm the most consistent predictors of stroke recurrence – advanced age and diabetes mellitus – and our nationwide study establish an inverse relationship between SES and stroke recurrence. Despite the overall declining incidence rates of stroke in Sweden, this inverse relationship has persisted over the study period and the same association is seen in Swedish men and women. Future research on secondary prevention will need to take into account targeted risk groups of patients to prevent stroke recurrence. A readily accessible intervention is to ensure that all stroke patients, regardless of SES, get equal access to secondary preventative measures.

AT treatment, both at time of and following ICH, is increasingly common in Swedish patients. Predictors of AC treatment in Swedish ICH survivors with concomitant AF are somewhat different from those of the general recommendations regarding when to prescribe ACs to AF patients. Still, many patients with compelling indications for AT treatment are not prescribed such agents.

The choice to treat AF patients with ACs following ICH has been beneficial to the patients studied here. Awaiting results from RCTs, the optimal timing of such treatment seems to be around 7–8 weeks following ICH. However, there are important limitations to observational studies on medical interventions that must be taken into consideration. For example, we did not have information on additional factors that are most certainly considered by clinicians when determining whether or not to treat. Still, our results are reassuring in the sense that clinical practice in Sweden regarding this patient group seems to have reduced the overall risk of severe subsequent events. Our results need confirmation in RCTs, but they also emphasize the need of observational studies to identify potential improvement areas in the treatment of vulnerable patients groups, often with chronic or disabling diseases.

Summary of conclusions

- ✓ Population-based risk factors for stroke recurrence are advanced age and diabetes. The overall risk of recurrence has decreased over the last two decades, in line with other studies from high-income countries.

- ✓ The use of antithrombotic drugs in ICH patients, both at the time of ICH and following discharge, has increased in Sweden. Predictors of AC treatment in AF patients following ICH are younger age, previous ischemic stroke, AC at the time of ICH and valvular disease.

- ✓ In ICH survivors with concomitant AF, the use of ACs in clinical practice seems beneficial, and the optimal timing of onset of treatment appears to be at around 7–8 weeks following the ICH.

- ✓ Low educational and low income levels, as well as living alone increase the risk of stroke recurrence in Swedish stroke patients. The inverse relationship between SES and recurrence risk is the same in men and women and has not changed over the last decade.

Future perspectives and personal reflections

Aside from presumed explanatory factors of the positive trends in Swedish stroke recurrence rates discussed above, this thesis has also imposed the question of whether clinical decisions, sometimes made despite lack of recommendations in national guidelines, have favorably affected the risk of stroke recurrence over the study period. To me, this work has thus been a reminder that the science and art of medicine intersect when there is not enough evidence to firmly guide physicians in the sometimes extremely challenging situation of weighing risk against benefit. There are most likely other, on-going, and perhaps unidentified, changes in clinical practice that will be important for future developments of successful secondary preventative measures in vulnerable patient groups. Finding these new, successful strategies will likely be important for a continuation of the favorable trends in stroke incidence and recurrence rates observed in Sweden. Riksstroke, both in facilitating observational studies and in providing publically available inter-hospital comparisons has, and will continue to play a pivotal role.

There seems to be a need for further identifying high-risk groups to prevent stroke morbidity and mortality, especially because these groups of patients sometimes fall behind when new promising treatments are introduced. Furthermore, our results on SES and risk of stroke recurrence need to be verified in other countries with different socioeconomic compositions.

The work with this thesis has also enhanced my recognition of the complimentary roles of observational studies and RCTs. None of the patient profiles (AF patients surviving ICH) would have been eligible in any of the RCTs of NOACs launched in the past decade. Emerging observational evidence on beneficial effects of AC even in traditional high-risk patient groups may have paved the way for future and on-going important trials.

Acknowledgements

I wish to express my warmest gratitude to all of those who helped me to complete this thesis. In particular, I would like to thank the following:

Participants in MONICA and Riksstroke and the health care personnel working with the registries, for making this research possible.

Marie Eriksson, my supervisor and mentor, for your inspirational scientific approach, for your expertise in statistics and stroke epidemiology and for your endless support (and patience) throughout my research education.

P-G Wiklund, co-tutor, co-writer, colleague and friend, for once introducing me to the exciting world of stroke research and for your highly valued support throughout both my clinical and scientific work.

Bo Carlberg, co-tutor, co-writer and colleague, for your much appreciated support and wisdom.

Kjell Asplund, co-writer and former stroke lecturer, for being such an inspirational role model and for invaluable support and input throughout my work.

Rosanna Overholser and Bart van Rompaye, co-writers and statisticians, for your excellent modeling, for making statistics comprehensible and for nice conversations also on other matters along the way.

Eva-Lotta Glader, co-writer and colleague, for your valuable support and calming advice.

Signild Åsberg, Aase Wisten and Bo Norrving, for much appreciated input as co-writers.

Gunborg Rönnberg, Åsa Johansson and Åsa Olofsson, for your patient assistance in helping me understand the registration procedures of MONICA and Riksstroke.

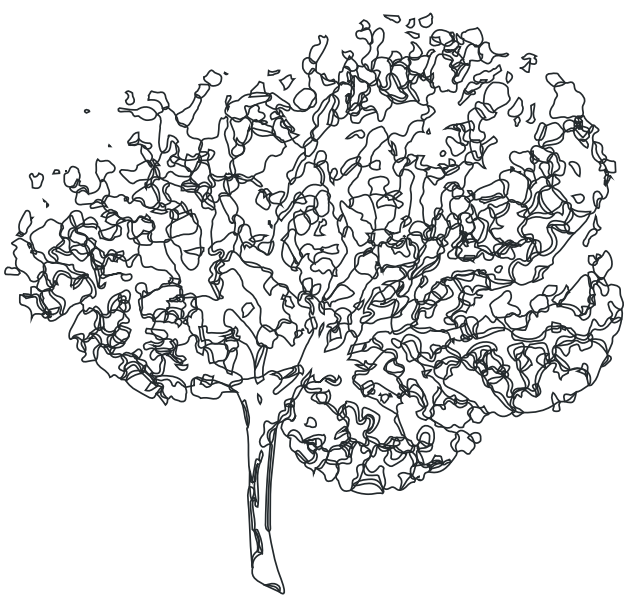
Colleagues and friends at the Norrland University Hospital and at the Department of Public Health and Clinical Medicine, for creating a supportive work environment and for encouraging words along the way.

All lovely friends outside work, for making me believe in myself and enjoying the lovely ride of life together with my family and me.

Emma, for your genius brain-tree.

Dad, mum and Fernando, my role models in life and parenthood and my sisters Lina and Julia, for showing me what great sisterhood can be.

Andreas, William, Signe and Ellen, my loved ones. You are the most important source of inspiration in life, in all the great and little things. I love you.



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