Serious hemorrhage and secondary prevention after stroke and TIA

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"Någon älskare av piller är jag inte men jag förstår att vetenskapen vet vad som är bra för mig och ändrar där det behöver ändras."

Birgit, deltagare i NAILED-studien
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Abstract

**Background** The number of stroke survivors is growing worldwide, and these patients have an increased risk of new vascular events and death. This risk decreases with secondary treatment medications recommended in guidelines. However, the characteristics of unselected stroke patients differ from patients included in randomized controlled trials (RCTs). Thus, the efficacy of these treatments based on RCT results may not be directly transferable to the patients treated in clinical practice. A treatment may be associated with a higher risk of serious side-effects or less benefit than expected: 1) Antithrombotic treatment increases the risk of a serious hemorrhage, a risk that is not well studied in an unselected population with older age and more comorbidities; 2) Treatment of modifiable risk factors after a stroke can be improved. Many patients do not reach treatment targets, which indicates a need for strategies to improve secondary prevention and increase treatment benefit. It is therefore essential to evaluate recommended treatments through studies in a real-world setting.

**Aims** The aims of this thesis were to assess incidence, temporal trends, effect on mortality, and factors associated with an increased risk of a serious hemorrhage after ischemic stroke (IS) or transient ischemic attack (TIA); and if a nurse-led, telephone-based intervention including medical titration could improve modifiable risk factors in patients after stroke or TIA.

**Methods** In paper I, all patients registered with an IS in the national stroke register Riksstroke during 1998–2009 were studied. The register was combined with the In-Patient Register and a diagnosis of intracranial haemorrhage (ICrH) within 1 year after IS was identified. In paper II, any diagnosis of serious hemorrhage was identified during follow-up up to 2015 in all patients with an IS or TIA diagnosis, 2010–2013, at Östersund hospital. The incidences of ICrH (papers I and II) and all serious hemorrhages (paper II) were calculated. Kaplan–Meier analysis was used to assess any temporal trend in paper I and if a serious hemorrhage affected survival in study II. Cox regression analysis was used in both studies I and II to assess any factor associated with hemorrhage.

In the randomized controlled NAILED stroke trial, all patients with acute stroke or TIA treated at Östersund hospital during 2010–2013 were screened for participation. Patients whose condition permitted a telephone-based follow-up were randomized to either a control group with follow-up according to usual care or to an intervention group with a nurse-led, telephone-based follow-up including titration of medication. Blood pressure (BP) and low-density lipoprotein cholesterol (LDL-C) were assessed at 1, 12, 24, and 36 months. We assessed the effect of the intervention on mean levels of BP and LDL-C and on the proportion
of patients reaching treatment targets at 12 months (Study III) and at 36 months
(Study IV). Study III also assessed for interactions between group allocation and
measurement levels at baseline with BP and LDL-C at the 12-month follow-up.
Study IV also explored temporal trends.

Results

The risk of an ICrH was 1.97% per year at risk, within the first year after IS, and
0.85% excluding the first 30 days. Between 1998 and 2009, the risk of an ICrH
increased during the first 30 days after an IS but decreased during days 31–365.
The risk of a serious hemorrhage was 2.48% per year at risk in paper II. It was
more common in elderly. The incidence rate was higher in patients discharged
with AP compared with RCTs. A hemorrhage increased the risk of death in
patients with good functional status but did not affect the already high mortality
in patients with impaired functional status. Male sex and previous ICrH were
associated with an increased risk of ICrH during the first year after IS,
thrombolytic treatment, atrial fibrillation and warfarin were associated with an
increased risk in the acute phase. A previous diagnosis of hypertension was
associated with an increased risk of all serious hemorrhages.

The NAILED trial intervention group had a significantly lower mean systolic BP
(SBP), diastolic BP (DBP), and LDL-C at 12 and 36 months. The mean SBP at 36
months was 128.1 mmHg (95% confidence interval (CI): 125.8–130.5) in the
intervention group, 6.1 mmHg (95% CI: 3.6–8.6; p<0.001) lower than the control
group. The interaction analysis at 12 months showed that the effect of the
intervention was confined to patients whose values were above the respective
targets at baseline and therefore had their medication adjusted. At 36 months, a
significantly higher proportion of patients in the intervention group reached
treatment targets for SBP, DBP, and LDL-C. The mean differences and
differences in proportions reaching treatment target for BP increased during the
36 months of follow-up.

Conclusion

A serious hemorrhage after an IS or TIA is fairly common. It is more common in
elderly and patients with impaired functional status. The incidence is higher in
patients discharged with AP compared with RCTs. A serious hemorrhage could
affect survival in patients with good functional status. The nurse-led, telephone-
based intervention including medical titration used in the NAILED stroke trial
improved risk factor levels after stroke and TIA, and more patients reached
treatment targets. The effect increased over time.
Original papers

This thesis is based on the following papers, referred to in the text by their Roman numerals (I-IV). The papers are appended in the end of this thesis.


### Abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AC</td>
<td>Anticoagulant</td>
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<tr>
<td>AP</td>
<td>Antiplatelet</td>
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<td>AF</td>
<td>Atrial fibrillation</td>
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<td>ASA</td>
<td>Acetylsalicylic acid</td>
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<td>AT</td>
<td>Antithrombotic (i.e., anticoagulants and antiplatelets)</td>
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<td>BMI</td>
<td>Body mass index</td>
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<td>BP</td>
<td>Blood pressure</td>
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<td>CDR</td>
<td>Cause of Death Register</td>
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<td>CI</td>
<td>Confidence interval</td>
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<td>DAPT</td>
<td>Dual antiplatelet therapy</td>
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<td>DBP</td>
<td>Diastolic blood pressure</td>
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<td>GI</td>
<td>Gastrointestinal</td>
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<td>GP</td>
<td>General practitioner</td>
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<tr>
<td>HR</td>
<td>Hazard ratio</td>
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<td>ICD</td>
<td>International Classification of Diseases</td>
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<td>ICH</td>
<td>Intracerebral hemorrhage</td>
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<td>ICrH</td>
<td>Intracranial hemorrhage</td>
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<td>IPR</td>
<td>In-patient register</td>
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<td>IS</td>
<td>Ischemic stroke</td>
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<td>K-M</td>
<td>Kaplan–Meier</td>
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<td>LDL-C</td>
<td>Low-density lipoprotein cholesterol</td>
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<td>mRS</td>
<td>Modified Rankin scale</td>
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<tr>
<td>NAILED</td>
<td>Nurse based Age independent Intervention to Limit Evolution of Disease after stroke or TIA</td>
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<td>NOAC</td>
<td>Non-vitamin K antagonist oral anticoagulant</td>
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<td>NPR</td>
<td>National Patient Register</td>
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<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>PIN</td>
<td>Personal identification number</td>
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<td>PPV</td>
<td>Positive predictive value</td>
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<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>PRoFESS</td>
<td>Prevention Regimen for Effectively Avoiding Second Strokes</td>
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<td>PROGRESS</td>
<td>Preventing Strokes by Lowering Blood Pressure in Patients with Cerebral Ischemia</td>
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<td>RCT</td>
<td>Randomized controlled trial</td>
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<td>RRR</td>
<td>Relative risk reduction</td>
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<td>SAH</td>
<td>Subarachnoid hemorrhage</td>
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<td>SBP</td>
<td>Systolic blood pressure</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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<td>SPARCL</td>
<td>Stroke Prevention by Aggressive Reduction in Cholesterol Levels</td>
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<td>SPS3</td>
<td>Secondary Prevention of Small Subcortical Strokes</td>
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<tr>
<td>TIA</td>
<td>Transient ischemic attack</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Sammanfattning på svenska

Vid en stroke skadas hjärnan på grund av syre- och näringsbrist orsakat av påverkad cirkulation på grund av en propp eller blödning. En blodpropp är orsaken i ca 85% av fallen, så kallad ischemisk stroke. Vid sytomen vid stroke men där symtomen försvinner inom ett dygn talar man om en TIA. En TIA innebär en ökad risk för att få en stroke.

Varje år drabbas drygt 25 000 svenskar av en stroke och ca 10 000 av en TIA. Var fjärde person med en stroke har haft det tidigare. Det är färre som dör i samband med en stroke och andelen i varje åldersgrupp som får en stroke i Sverige minskar förutom hos de yngsta. Efter en stroke eller TIA är risken stor för död, bestående handikapp eller en ny stroke.

Flera så kallade riskfaktorer ökar risken för att få en stroke. Vissa, så som hög ålder och manligt kön går inte att påverka. Andra, som till exempel förhöjt blodtryck, höga blodfetter, rökning, inaktivitet och förmaksflimmer är faktorer som kan påverkas och livsstilsförändringar och/eller läkemedel kan minska risken. Stroke och TIA patienter skrivs därför ut med läkemedel i syfte att minska risken för ny stroke eller TIA och denna avhandling fokuserar på denna behandling, så kallad sekundär prevention. Jag har studerat två olika delar av denna behandling:

1) Efter en ischemisk stroke eller TIA får patienter med förmaksflimmer antikoagulantia för att minska risken för en ny propp medan övriga patienter får trombocythämmare i samma syfte. Båda dessa ökar risken för blödning men i de läkemedelsstudier som behandlingsriktlinjer baseras på är nytta i form av minskad risk för nya blodproppar klart större än risken för blödning. Deltagarna i dessa studier är ofta yngre och friskare jämfört med patienter på en strokeavdelning och därför undersöktes risken för allvarlig blödning, inklusive intrakraniell blödning, som har högst dödlighet, i en oselekterad sjukhuspopulation.


Risken för en intrakraniell blödning var ca 2% under det första året. Risken var 0.9% efter den akuta fasen, vilket var ca 15 gånger mer än i en referenspopulation.
Mellan 1998 – 2009 minskade risken för intrakraniell blödning efter den akuta fasen något, trots att fler blev utskrivna med blodförtunnande läkemedel. Risken för all allvarlig blödning inklusive intrakraniell blödning var cirka 2,5% per år. För patienter utskrivna med antikoagulantia är den risken i nivå med den som visas i läkemedelsstudier medan den var mer än dubbelt så hög för all allvarlig blödning för de som skrivits ut med trombocythämmare jämfört med läkemedelsstudier. Vi såg en högre andel med blödning bland de som var över 75 år liksom bland de som hade betydande kvarstående symtom efter sin stroke. Dessa grupper är sällan representerade i stora läkemedelsstudier vilket skulle kunna förklara skillnaden mellan min studie och läkemedelsstudier. Dödligheten efter en stroke skiljer sig beroende på vilken funktionsnivå patienten har vid utskrivning. Av de som skrevs ut med en bra funktionsnivå avled 18% av patienterna under de närmaste fem åren och en allvarlig blödning ökade risken för död. Av patienter med betydande hjälpbehov efter sin stroke avled 59% inom fem år och en allvarlig blödning påverkade inte prognosen.

Sammanfattningsvis påvisades en ökad blödningsrisk efter en stroke eller TIA. Risken var högre hos de som blev utskrivna med trombocythämmare jämfört med läkemedelsstudier. Risken var högre hos äldre och patienter med betydande handikapp. Samtidigt är risken för nya propar högre hos dessa patienter varför vi inte kan avgöra om balansen mellan risk och nytta är påverkad. Cirka 40 % av strokepopulationen är över 80 år och med den osäkerhet som finns kring behandling av dessa patienter finns ett behov av fler studier för att undersöka risk jämfört med nytta vid trombocythämmande behandling.


Samtliga patienter vårdade för stroke eller TIA på Östersunds sjukhus 2010–2013 som bedömdes kunna klara av ett telefonsamtal tillfrågades om att delta i studien. Hälften av de som accepterade att delta lottades till en kontrollgrupp med uppföljning enligt gällande rutin i primärvården, medan den andra hälften lottades till interventionsgruppen, med uppföljning enligt studiemetoden. Blodtryck och blodfetter undersökeses vid 1, 12, 24 och 36 månader efter utskrivning och deltagarna kontaktades efter varje uppföljning av en studiesköterska för återkoppling, samtal om läkemedelsanvändning, levnadsvanor mm. Om blodtrycket eller blodfettarna inte nådde målvärde så
kontaktades en studieläkare för korrigerings av läkemedel och proceduren upprepades efter 4 veckor tills målen var uppnådda.

Den slutgiltiga uppföljningen efter 36 månader visade att interventionsgruppen hade ett systoliskt medelblodtryck på 128,1 mm Hg jämfört med 134,2 mm Hg i kontrollgruppen. Det diastoliska medeltrycket samt blodfettvärdet LDL-C var också tydligt lägre i interventionsgruppen samt andelen som nådde målvärde för blodtryck och LDL-C högre. Skillnaden mellan de två grupperna ökade under hela studietiden för blodtryck medan den skillnad som uppnåddes vid 1 år för LDL-C kvarstod oförändrad. Nästan all va dock i behov av justering av läkemedelsbehandling vid något tillfälle under studietiden och många som hade ett bra värde vid en uppföljning kunde ha hamnat över målvärde vid nästa uppföljning. Sammanfattningsvis visar dessa studier att den sköterske- och telefonbaserade interventionen med möjlighet till läkemedelsjustering leder till lägre blodtryck och blodfetter samt att fler når aktuella målvärden. Det finns ett behov av kontinuerlig långsiktig uppföljning även om man vid ett tillfälle nått målvärde.
Introduction

Stroke is a serious event associated with increased risk of death, disability, and new events. Prevention with lifestyle changes and medication to reduce the risk of a recurrent stroke event (secondary prevention) is an important part of stroke care. This thesis focuses on prognosis after stroke or transient ischemic attack (TIA) in terms of hemorrhage, a feared condition and potential side effect of antithrombotic (AT) treatment and on optimized implementation of secondary preventive treatment.

Etiology and Pathophysiology

The World Health Organization (WHO) defines stroke as “rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, with symptoms, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin”¹. Thus, the origin of a stroke is vascular, caused by an occlusion (ischemic) or rupture (hemorrhagic) of a cerebral vessel. Both subtypes result in lack of oxygen and nutrients to the brain, causing damage and symptoms that depend on where the brain is damaged.

Transient ischemic attacks (TIAs) are “episodes of temporary and focal cerebral dysfunction of vascular origin, rapid in onset [...] are variable in duration, commonly lasting 2 to 15 minutes [...] Each attack leaves no persistent neurological deficit”². Improved imaging techniques have shown that a considerable number of TIA patients actually have an irreversible brain lesion³-⁴. The International Classification of Diseases (ICD), maintained by the WHO, is the most used classification system worldwide. In the 11th edition of the ICD (ICD-11), the TIA definition was changed from a time-based definition to a tissue-based one. ICD-11 was released in 2018 and will be implemented over the coming years, but for this thesis, all definitions of TIA and codes used for cerebrovascular diseases and other conditions are according to the 10th edition (ICD-10)⁵.

The mechanisms underlying the arterial occlusion that leads to an ischemic stroke (IS) or TIA are heterogeneous. Thus, the secondary preventive strategies described below can differ depending on cause. The etiologies of IS and TIA are often divided into large-artery atherosclerosis, cardioembolism including atrial fibrillation (AF), small-vessel occlusion, stroke of other determined etiology including arterial dissection, and stroke of undetermined etiology⁶-⁷. Large-artery atherosclerosis, cardioembolism, and small-vessel occlusion are the causes in most IS and TIA cases, but in a considerable portion, the cause remains undetermined⁸-⁹. Cardioembolism as the etiology increases with age, whereas the
category of other determined etiology constitute the larger proportion in younger stroke patients\textsuperscript{9}.

In a hemorrhagic stroke caused by a vessel rupture, the hemorrhage could either be into the brain parenchyma (an intracerebral hemorrhage; ICH) or into the subarachnoid space (subarachnoid hemorrhage; SAH). Epidural and subdural hemorrhages are forms of intracranial hemorrhage (ICrH) that are not included in the stroke definition\textsuperscript{10}. The vast majority of all ICHs are situated in the deep parts of the brain or in the brainstem (deep ICH) or are more superficially located (lobar ICH). A deep ICH is most often associated with the same vessels as in ischemic small vessel disease, while the lobar ICH is associated with deposition of B-amyloid in the vessels (cerebral amyloid angiopathy)\textsuperscript{11}. In the national stroke register Riksstroke, 88% of all registered strokes are IS, and 12% are ICH\textsuperscript{12}.

**Epidemiology**

Stroke is the second leading cause of death globally. Although the age-standardized mortality rate decreases, the mean age is increasing worldwide, leading to a growth in absolute numbers of stroke deaths\textsuperscript{13, 14}. The temporal trends in different countries vary: incidence and mortality are falling in high-income countries but rising in low- and middle-income countries\textsuperscript{14, 15}. Sweden, where 26,500 people were discharged with a stroke diagnosis in 2016, shows the same trend as other high-income countries: a decrease (40% in Sweden) in the age-standardized incidence from 2002–2016\textsuperscript{16}. The incidence varies widely with age and is roughly 100 times greater among those 85 and older compared with people ages 35–44 years\textsuperscript{17, 18}; more than 80% of patients are 65 years and older\textsuperscript{19}. However, the falling incidence in the total population is not the pattern in people under age 65 years\textsuperscript{20}, with an upward trend among the youngest patients\textsuperscript{21, 22}.

**Risk factors**

Several factors change the risk of stroke. Unadjustable contributors are called non-modifiable risk factors and include age\textsuperscript{23} and male sex\textsuperscript{24, 25}, both of which increase the risk for IS and ICH. Modifiable risk factors are adjustable with lifestyle changes and/or medical treatment. Important modifiable risk contributors for both IS and ICH are hypertension, smoking, obesity, diet, inactivity, alcohol, diabetes, and psychosocial factors\textsuperscript{26}.

Hypertension is the premier risk factor for all stroke, both IS and ICH\textsuperscript{26}. The relationship between blood pressure (BP) and stroke is strong, continuous, and consistent across sexes, ages, regions, stroke subtypes, and fatal and non-fatal strokes\textsuperscript{27}. Also, treating high BP reduces stroke risk over a broad range of different subgroups\textsuperscript{28}. 
Two modifiable risk factors for IS but not ICH are cardiac source and dyslipidemia. The dominant cardiac source is AF; approximately 2.9% of the Swedish population has known AF, and prevalence increases with age. The risk of stroke is almost fivefold with AF. Serum cholesterol includes low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, and triglycerides. For cholesterol levels, higher levels are positively associated with stroke risk. However, the association with ICH is an inverse one, with lower levels increasing the risk of hemorrhage. Treatment of cholesterol levels in primary prevention reduces LDL-C and the risk of IS in a high-risk population without increasing the ICH risk.

**Prognosis**

After a stroke, risk of death or persistent disability climbs considerably. In Riksstroke, the 1-month and 1-year fatality rates are 15% and 23% after an IS. Corresponding rates after an ICH are 30%–40% and 37%–55%. Increasing age and decreased functional status increase the risk of death after stroke.

Following a stroke or TIA, the risk of a new stroke and other vascular events is high. The cumulative incidence of a recurrent IS the first year varies among different populations but is approximately 10%. About one in four strokes in Sweden is a recurrent event. The risk of a new stroke is equally common after an IS and an ICH. After an IS, a recurrent stroke is usually a new IS, although not necessarily of same etiological origin. An IS also is the cause in at least half of recurrent strokes after an ICH. The risk of stroke after a TIA is also increased. In a 2007 meta-analysis, it was at least 8% at 30 days after a TIA. A more recent multicentre study found a lower risk of 3% after 30 days and 5% after 1 year.

**Secondary prevention**

To reduce the increased risk of vascular events after stroke and TIA, patients are prescribed medical treatments according to guidelines. For all stroke and TIA patients, the recommendation is to treat hypertension. In patients with an IS or TIA, AT and lipid-lowering treatments are also recommended. The use of medical treatments in secondary prevention and their risks and possible benefits are the foundation of this thesis and described below.

**Antithrombotic treatment**

In the absence of contraindication, mainly high risk of hemorrhage, guidelines recommend AT treatment for all patients with an IS or TIA. The type of AT treatment depends on the stroke etiology; anticoagulant (AC) treatment is recommended for patients with AF and antiplatelets (APs) for those without AF.
**Antiplatelets**
For recurrent stroke, with AP therapy with acetylsalicylic acid (ASA) compared with placebo, the relative risk reduction (RRR) is 15%\(^49\). The RRR for a new vascular event with any AP compared with placebo was 22% in a 2002 meta-analysis\(^50\). The effect of adding dipyridamole to ASA is slightly greater than with ASA alone (absolute risk reduction, 1% for new vascular events compared to ASA alone)\(^51\), and the effect of clopidogrel is comparable to the combination of ASA and dipyridamole\(^52\). All three alternatives have been used in parallel during the period of this thesis and considered as alternatives in guidelines\(^46, 47, 53\).

More recent trials investigating the effect of dual antiplatelet therapy (DAPT) with ASA + clopidogrel vs ASA after stroke and TIA have shown no benefit against recurrent stroke in patients with small vessel disease during long-term follow-up; however, they did find an increase in hemorrhages\(^54\). That said, two trials showed a reduction in new events among the DAPT group\(^55, 56\) after a minor stroke or TIA with use during a limited time of 1–3 months. However, these trials on DAPT published from 2012 to 2018 did not influence treatment in the population included in this thesis.

**Anticoagulants**
In patients with AF, AC treatment with warfarin decreases stroke risk, and in patients with ischemic stroke, the RRR is 68% with warfarin compared with placebo\(^57\). During the 2010s, non-vitamin K antagonist oral anticoagulants (NOACs) were introduced\(^58-60\) as alternatives to warfarin. The NOACs were associated with the same rate of new vascular events as warfarin in participants with prior stroke or TIA\(^61-63\). ACs have been underused, especially in women and the elderly\(^29\), but the proportion of stroke patients discharged with ACs today has increased radically from approximately 20% and 50% in patients over and under age 80 years in 2000–2005 to almost 75% and >80% in 2017\(^64\).

**Risk for hemorrhage after IS and TIA**
Thus, AP or AC treatment is recommended for most patients after an IS or TIA. Both treatments carry an increased risk of hemorrhage. A history of vascular disease and IS increases the risk of ICH\(^65\). For ICrH, cases are few, or incidence rates are not reported in many randomized controlled trials (RCTs). In a recent RCT of NOACs, ICrH incidence rates were 0.8%–1.4% per year at risk in patients using warfarin and with a recent stroke\(^61-63\) and 0.2%–0.4% per year at risk in patients with single or double AP treatment (the SPS3 trial)\(^54\). For all serious hemorrhage, the risk of a serious hemorrhage varies in RCTs between 2%–5% per year at risk in patients treated with warfarin and 1%–2% for different AP regimens\(^54, 61-63, 66-70\). Participants in these RCTs were younger, 59–70 years, and with less comorbidity than patients in clinical practice. Smaller observational studies in patients with stroke report only a few cases with serious hemorrhage\(^71-\)
In a Swedish registry study, the incidence rates of serious hemorrhage were 2.5% and 2.4% for AC and AP treatment, respectively. The incidence in patients treated with AP was higher than in the RCTs, and the patients in the study had a mean age of 75 years; age was an apparent factor associated with increased risk. Of all hemorrhages, ICrH is the most feared. In one study, a reported 76% of patients with a warfarin-caused ICrH died or became disabled, whereas only 3% of patients with extracranial hemorrhages did so. The incidence and fatality of gastrointestinal (GI) hemorrhages also increases with age.

**Antihypertensive treatment**

Treating hypertension reduces the risk of new events after stroke and TIA. A meta-analysis of RCTs on BP treatment after stroke showed a mean BP reduction of 5.1/2.5 mmHg in the treatment arm, with a 22% RRR for recurrent stroke. The question has been when to treat and to what target. The PROGRESS trial, included in the same meta-analysis, showed an effect of BP reduction down to 120 mmHg regardless of baseline pressure. In a post-hoc analysis on another RCT, PROFESS, showed an increased risk of recurrent stroke in patients with a BP <120 mmHg. However, the only trial so far on secondary treatment in stroke patients that has randomized patients to different treatment targets with reduction in stroke as primary endpoint is the SPS3 trial. In this trial, patients were randomly allocated to a target of <130 mmHg or 130–149 mmHg, and the results showed a small but not significant effect in the intensive target group.

Guidelines recommend treatment of hypertension and that normotensive patients can be considered for treatment. The treatment target varies but should be at least <140/90 mmHg, but lower targets could be considered in some cases.

**Lipid-lowering treatment**

In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, the only trial designed for secondary prevention in stroke patients, the RRR for new stroke was 22% and the RRR for new major coronary events was 35% in patients treated with high-dose statin; both values were significant. The included patients were stroke patients with a non-cardioembolic stroke. There was an increased risk of ICH in the treatment arm that could not be confirmed in meta-analysis with patients on secondary prevention from other trials. Guidelines recommend statins, but the recommendation varies. No study has investigated what the treatment target should be. Since 2012, the treatment target has been 1.8 mmol/L in European and later specifically Swedish guidelines; however, in US guidelines, it was changed from the same target to a high-dose regimen with no specific target in 2014.
Addition of PCSK9 inhibitors or ezetimibe to statins further reduces LDL-C and could possibly decrease new events in stroke patients\(^{86, 87}\). So far, though, these combinations have not been used in any trial focused on secondary prevention in stroke patients.

**Secondary prevention in clinical practice**

Although the effect of secondary prevention treatments on new events after stroke is proven in RCTs and recommended in guidelines, many patients do not receive these treatments\(^{88-90}\), especially elderly patients\(^{88, 90}\), or stop taking the medicines soon after their stroke\(^{91, 92}\). Taking medicine or not, many patients do not reach treatment targets. In observational studies, only 25%–49% of all patients reach their treatment target for BP and 14%–77% for LDL-C\(^{93-97}\).

Thus, interventions and methods are needed to improve modifiable risk factors. Several published studies have focused on this need, but the methods, outcomes, follow-up periods, and results are heterogeneous\(^{97-110}\). In a meta-analysis that allocated studies into two broad groups, educational interventions were not associated with any differences in outcomes. However, interventions at the organizational level were associated with improvements in BP achievement targets but with non-significant improvements in BP levels\(^{111}\) and no effects on lipid profile. Some programs associated with improved BP levels included the possibility of titrating medical treatment\(^{104, 105, 108}\). Despite long-term increased risk for new events after a stroke\(^{37, 40}\), few of the intervention studies had follow-up beyond 12 months, and any effect seemed to decline over time\(^{99, 110}\).

Considering the high prevalence of stroke survivors and limited available resources for public health care, a long-term, cost-effective intervention to improve secondary prevention after stroke or TIA would be desirable. Involving health care professionals other than physicians and the use of telemedicine might be two strategies to achieve this aim.
Summary of introduction

- Stroke is a common cause of death and disability worldwide. The age-specific stroke-associated mortality is decreasing globally. In Sweden, the incidence in most age categories also is falling, but many low- and middle-income countries have seen increases. With decreasing mortality, the numbers of stroke survivors are growing.

- Stroke survivors are at increased risk of new events. To reduce the risk, most stroke and TIA patients are discharged with secondary prevention according to guidelines that are based on RCTs.

- Participants in RCTs do not always reflect patients in real-world clinical practice. RCT patients are often younger and have fewer comorbidities. AT treatment increases the risk of hemorrhage, and the risk–benefit ratio might be different in an unselected stroke and TIA population.

- Many patients do not reach treatment targets for BP and LDL-C. A new strategy to improve follow-up and use the full potential of antihypertensive and lipid-lowering treatments is needed.
Aims

The aims of this thesis were as follows:

I – To assess the risk of ICrH within 1 year after an IS in an unselected population, identify factors associated with an increased risk of ICrH, and determine if the risk changes over time.

II – To assess the risk of serious hemorrhage after IS and TIA in an unselected population, identify factors associated with an increased risk of a serious hemorrhage, and study if a serious hemorrhage affects survival.

III – To investigate if a nurse-led, telephone-based follow-up including pharmacological titration is more efficient than usual care at improving risk factor levels in short-term follow-up after stroke or TIA.

IV - To investigate if a nurse-led, telephone-based follow-up including pharmacological titration is more efficient than usual care at improving risk factor levels in long-term follow-up after stroke or TIA and to explore trends over the study period.
Table 1 summarizes the study design, population, and outcomes for the four studies included in this thesis. Details on data sources and specific details on methods used for outcome assessments are described below.

### Table 1 - Study design and population, papers I-IV

<table>
<thead>
<tr>
<th>Paper</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of study</strong></td>
<td>Hospital-based cohort study</td>
<td>Hospital-based cohort study</td>
<td>RCT</td>
<td>RCT</td>
</tr>
<tr>
<td><strong>Data source</strong></td>
<td>Riksstroke, IPR, National Civil register</td>
<td>NAILED – screening phase, local IPR</td>
<td>NAILED</td>
<td>NAILED, CDR</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>196,765</td>
<td>1528</td>
<td>537</td>
<td>660</td>
</tr>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td>IS</td>
<td>IS or TIA</td>
<td>Stroke (IS/ICH) or TIA and able to participate in a telephone-based follow-up</td>
<td>Stroke (IS/ICH) or TIA and able to participate in a telephone-based follow-up</td>
</tr>
<tr>
<td><strong>Follow-up time</strong></td>
<td>12 months</td>
<td>Discharge - 31 Dec 2015</td>
<td>12 months</td>
<td>36 months</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>1) Incidence of ICrH after IS</td>
<td>1) Incidence of serious hemorrhage after IS and TIA</td>
<td>1) Mean difference in SBP, DBP, and LDL-C between intervention and control groups</td>
<td>1) Mean difference in SBP, DBP, and LDL-C between intervention and control groups</td>
</tr>
<tr>
<td></td>
<td>2) Difference in incidence over the study period</td>
<td>2) Difference in survival with or without serious hemorrhage</td>
<td>2) Difference in proportion reaching treatment target for SBP, DBP, and LDL-C between intervention and control groups</td>
<td>2) Difference in proportion reaching treatment target for SBP, DBP, and LDL-C between intervention and control groups</td>
</tr>
<tr>
<td></td>
<td>3) Factors associated with ICrH after IS</td>
<td>3) Factors associated with serious hemorrhage after IS or TIA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Data sources**
The almost 100 nationwide quality registers in Sweden today collect information on background, diagnosis, treatment, and outcome for different disorders to provide feedback and stimulate improvements in the quality of health care.112
Also, Swedish authorities such as the National Board of Health and Welfare and Statistics Sweden maintain nationwide registers. Information from linking these registers can serve as the foundation for register-based research. The linking is made possible by the unique personal identification number (PIN) that each resident in Sweden has. The Swedish Tax Agency is responsible for maintenance of civil registration\textsuperscript{113}. The registers used in this thesis are described below, and Table 1 describes which papers used specific registers.

**Riksstroke**
Riksstroke is the Swedish national quality register for stroke care. It was established in 1994 and is the world’s longest running stroke register\textsuperscript{114}. Patients eligible for registration are diagnosed with IS (ICD-10 code I63), ICH (I61), or an unspecified acute cerebrovascular event (I64). Since 1998, all hospitals in Sweden admitting stroke patients report to the register. Riksstroke contains data on age, sex, cardiovascular risk factors, drug therapy, and dependency in activities of daily living. Cardiovascular risk factors comprise diabetes mellitus, AF, hypertension, and smoking history.\textsuperscript{115} Until 2004, Riksstroke registered only AT drugs, but statins and antihypertensive drugs since have been included. The numbers of stroke patients registered and the coverage increased during the first years of the register and were stabilized around 2003\textsuperscript{114}. Until 2006, the coverage assumed that the stroke incidence was (250–)300 per 100,000 years at risk, while the coverage after 2007 was calculated by dividing numbers registered in Riksstroke with those registered in the National Patient Register (NPR) (described below). The coverage was approximately 80% in 2000 and 85% in 2009. However, because of false-positive diagnoses of stroke in NPR\textsuperscript{116}, the method used after 2007 probably underestimates the coverage, which could be above 90%\textsuperscript{117}. Patient groups at risk of not being included are those who die early, who are not treated at a stroke unit, or who receive care in a nursing home\textsuperscript{118}.

**National Patient Register**
The Swedish In-patient Register (IPR) is a part of the NPR, maintained by the National Board of Health and Welfare. The IPR contains data for all inpatient care in Sweden with variables on admission and discharge date and primary and secondary diagnoses at discharge. Caregivers in Sweden are required to report to the register, and since 1987, it has contained data for all in-patient care in Sweden\textsuperscript{119}. The register has been validated in multiple studies and has a positive predictive value (PPV) for stroke of 98.6% and sensitivity of 84%–98%\textsuperscript{120}. The PPV is lower for a recurrent stroke event and for fatal stroke cases\textsuperscript{116}, as is the sensitivity.
**The Swedish Cause of Death Register**

The Cause of Death Register (CDR) is also maintained by the National Board of Health and Welfare. The register is updated annually and contains data for deaths of all Swedish citizens since 1952. The data, based on death certificates, include date and cause of death and the underlying and contributing causes of death based on the ICD system. All deaths are reported, but a small proportion (0.9% in 2015) are missing an underlying cause of death\(^1\). The specificity of the CDR is lower than for the IPR\(^2\)-\(^4\). A 2009 study showed that the underlying cause of death in hospital deaths was correct in CDR in 77% of cases but in only 68% of cerebrovascular disease cases\(^5\).

**Statistics Sweden and National Civil Registry**

For comparing the risk of an ICrH after ischemic stroke with the risk in a general population in paper I, a reference population was used. The administrative authority Statistics Sweden created the population by matching each patient in Riksstroke (1:1) to an individual of the same sex, age, and county of residence in the National Civil Registry. Data from the IPR were then obtained for the reference population. The matching was made by January 1 of the year of the index stroke in the corresponding stroke patient. Therefore, some of the patients in the reference group died before the index event and had to be excluded (n=5763). It was also impossible to find a matching control in some cases (n=845). The reference group is therefore smaller than the Riksstroke population.

**NAILED**

All patients treated for an ICH, IS, or TIA at Östersund hospital between January 1, 2010, and December 31, 2013, were screened and considered for participation in the Nurse-based Age-independent Intervention to Limit Evolution of Disease after stroke or TIA (NAILED) stroke trial (flow chart, Figure 1). The identification of patients with a stroke or TIA was made by study nurses through daily review of the stroke unit and of all patients undergoing a computed tomography brain scan at the hospital. The final stroke or TIA diagnosis was made by physicians not involved in the study. Study nurses collected all baseline data for all stroke and TIA patients during the screening process. All patients in a condition permitting a telephone-based follow-up were considered eligible for the intervention part of the trial and offered to participate. Patients with aphasia, impaired hearing, cognitive impairment, or severe, often terminal disease were therefore excluded.

All eligible and consenting patients were randomized 1:1 to either the intervention or control group and stratified for sex and for degree of disability (modified Rankin Scale (mRS) <3 or ≥3). Allocation was not blinded to participants, study
team, or other caregivers. The mRS were estimated and registered by study nurses at discharge.

**Follow-up and intervention**
All participants in the intervention trial were contacted to measure BP and blood lipids at 1, 12, 24, and 36 months. The measurements were performed at the patient’s nearest health station and reported to the study team. BP was measured in a seated position after 5 minutes of rest, and LDL-C was calculated using the Friedwald formula. A BP <140/90 mmHg and LDL-C <2.5 mmol/L (1.8 mmol/L in patients with diabetes in measurements after March 31, 2013) was considered within treatment target in the NAILED stroke trial.

![Flow of participants in NAILED stroke trial](image)

*Figure 1 - Flow of participants in NAILED stroke trial*

Participants in the control and intervention groups were contacted shortly after the measurements by a study nurse and asked systematically according to the variables in the study protocol about sense of well-being, tobacco use, physical
activity, and persistence to prescribed pharmacological treatment. Participants in the intervention group had lifestyle counselling. If the BP and/or lipid measurement did not reach treatment target, the study nurse contacted a study physician for evaluation and adjustment of the pharmacological treatment. The treatment was individualized to each participant and not fixed to any prespecified algorithm. For LDL-C, lipid-lowering treatment was synonymous with statins. A few were treated with ezetimibe when not reaching treatment target despite full-dose statin. After approximately 4 weeks, a new measurement was made in participants who did not reach target at baseline, and the procedure was repeated if necessary. Lipid-lowering treatment was restricted to participants with an ischemic stroke or TIA. BP and LDL-C measurement in the control group were forwarded to each participant’s general practitioner (GP) for further assessments. No evaluation of the pharmacological treatment was made by the study team, and the control group received no lifestyle counselling.

**Outcomes and statistical methods**

In all four studies, descriptive statistics such as means and proportions are presented. Comparisons between groups were made using the chi-square test for categorical variables and t-test for continuous variables. Outcomes and specific statistics used for each paper are presented below.

**Paper I**

Patients registered with an IS (ICD-10 code: I63) in Riksstroke 1998–2009 were included. In case of more than one registration, only the first event was used. Data from Riksstroke were combined with data from NPR. A reference population was also developed as described above.

**Outcomes:**
- Incidence rate and cumulative incidence of ICrH 0–30 and 31–365 days after an IS
- Time trends for ICrH 0–30 and 31–365 days after an IS
- Factors associated with the risk of an ICrH 0–30 and 31–365 days after an IS

We divided the follow-up period into two phases, 0–30 days after an IS and 31–365 days after IS, to reflect possible differences in mechanisms of ICrH in the acute phase. The patients were followed from their stroke and until ICrH, death, or end of follow-up, depending on which occurred first. The ICD-10 codes I60, I61, or I62 in the IPR were used to identify an ICrH. If more than one event of ICrH was found, only the first event was included.

Incidence rates was calculated for ICrH but also separately for ICH (ICD-10: I61). Kaplan–Meier (K-M) analysis, with the log-rank test for group comparisons, was

Cox proportional hazard (PH) regression analysis\(^{125}\) was used to explore factors associated with an increased risk of ICrH during days 31–365. It assess if one (uni-) or more (multi-) variables are associated with time to an event. An important assumption in this model is the PH assumption, i.e., the hazard ratio, the ratio between an exposed and an unexposed objects likelihood to experience an event, should remain unchanged during the time they are followed. The PH assumption was verified with K-M analysis in the univariable analysis and by examination of the Schoenfeld’s residuals in the final multivariable analysis. We have no knowledge on what day medication was withdrawn or started during hospitalization and we do not know on what day any ICrH occurred. This makes Cox PH regression analysis less suited during the acute period, so logistic regression analysis was performed to explore factors associated with an ICrH in the first 30 days.

In paper I, both the logistic and Cox PH regression multivariable models contained all variables from the univariable analysis to adjust for factors associated with vascular disease. However, for the results in the introduction to this thesis, we made changes to the multivariable Cox PH regression and logistic regression analysis for two reasons: 1) In paper I, age is a continuous variable, so to fulfil the PH assumption, age was changed from a continuous to a categorical variable; and 2) as a sensitivity analysis, we wanted to see if another approach changed the outcome in the multivariable analyses we used in paper II. In the introduction to this thesis, therefore, factors with a p-value <0.10 in the univariable model along with age and sex were included in a multivariable model. A second model was then made with all significant variables from the first multivariable model, age and sex. Some variables were added to Riksstroke in 2004, and to obtain a fairly complete dataset, the analysis of factors associated with an ICrH includes data from 2004–2009.

**Paper II**

All patients discharged from Östersunds hospital after hospitalization for an IS or TIA during 2010–2013 were included. Patients who died or experienced a serious hemorrhage during hospitalization were excluded. Patients were identified in the screening process of the NAILED stroke trial as described above. Events of serious hemorrhage were searched for in the local IPR. ICD-10 codes searched for are shown in Table 2. Data regarding date of death were obtained from CDR.
Outcomes:
- Incidence rate and cumulative incidence of serious hemorrhage after IS or TIA
- Risk of death after IS or TIA and if a serious hemorrhage affected the risk
- Factors associated with an increased risk of serious hemorrhage after IS or TIA

All hemorrhages were classified as ICrH, GI, or other. All observed hemorrhages, both primary and secondary diagnoses, were validated against the patient records and classified as serious if they were (1) an ICrH, (2) the main cause of admission, or (3) required transfusion or surgery. In case of more than one serious hemorrhage, only the first was included. The patients were followed from discharge until an event of serious hemorrhage, death, move out of the county, or end of follow-up on 31 December 2015, whichever occurred first.

Cumulative incidence was obtained using a competing risk approach instead of the ordinary K-M technique. This approach allows for multiple competing fatal events in relation to the one under investigation. A drawback with ordinary K-M analysis is that the risk of an event is the same in a censored patient (who is no longer observed for prespecified reasons) as in an observed patient. In this population, there was a high mortality, and taking the competing risk of death and other serious hemorrhages into account could give a more accurate description.

The risk of death was analysed with K-M analysis. Patients were divided into groups of good versus impaired functional status. Good functional status was defined as mRS 0–2 at discharge and impaired functional status as mRS 3–5. The effect of serious hemorrhage on mortality in the two groups was analysed, and the log-rank test was used for comparisons.

To identify factors associated with an increased risk of a serious hemorrhage, the Cox proportional hazards regression model was used. Factors with a p-value <0.10 in the univariable model along with age and sex were included in a multivariable model. Factors with a p-value <0.10 in this model, age and sex were included in the final model. This model was also performed with a competing risk analysis.

Table 2 - ICD-10 codes included in the screening for serious hemorrhage

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>D62.9</td>
<td>Acute post-hemorrhagic anaemia</td>
</tr>
<tr>
<td>D50.0</td>
<td>Iron deficiency anaemia secondary to blood loss</td>
</tr>
<tr>
<td>H11.3</td>
<td>Conjunctival hemorrhage</td>
</tr>
<tr>
<td>H31.3</td>
<td>Choroidal hemorrhage</td>
</tr>
<tr>
<td>H35.6</td>
<td>Retinal hemorrhage</td>
</tr>
</tbody>
</table>
Papers III and IV
Participants, eligibility criteria, and intervention in the NAILED stroke trial are described above. Paper III presents the results of the 12-month follow-up, and paper IV presents the results of the 36-month follow-up.

Outcomes
- Mean BP and LDL-C, differences from baseline and difference between groups
- Proportion reaching treatment target for BP and LDL-C

Participants who completed follow-up were analysed for outcomes. Paired sample t-tests were used to analyse mean differences between baseline (1-month measurement) and final follow-up within a single group. For mean value at last follow-up and difference between groups, a general linear model adjusted for sex and degree of disability, to reflect the randomization, was used as prespecified\textsuperscript{126}. In paper III, a second general linear model was used to assess if any difference between the groups was attributable to participants in the intervention group with a measurement value above treatment target at baseline. This model also included an indicator variable denoting if the participants were above or below treatment target at baseline. The model also contained an interaction variable between the treatment target variable and the treatment group allocation. Participants who did not complete the 36 months of follow-up were analysed for
any between-group differences, including death rates and cause of death, with information from the CDR.

SPSS versions 20.0, 22.0, and 24.0 and SAS version 9.4 (paper II) were used for the statistical analysis. A p-value of 0.05 was considered significant in all analyses.

**Ethical considerations**

All patients treated for stroke are informed that they will be registered in Riksstroke, that the register aims to develop and ensure the quality of stroke treatment in Sweden, and that the register might be used for research purposes. The patients are informed that they have the right to decline registration and that they can have the registered data erased at any time.

The unique PIN is the foundation of the register-based research and makes it possible to combine registers, but it is also a possible source of identification. To preserve the integrity of the patient, the PIN was removed before the data were delivered to us, and with more than 195,000 patients registered in the database, it is impossible to identify a unique person.

In papers III and IV, all participants received written and oral information about the NAILED stroke trial and then signed an informed written consent.

All studies were approved by the ethical review board in Umeå. Study using Riksstroke (paper I) on August 13, 2010 (Dnr: 2010-167-31M) and the NAILED study (papers II–IV) on October 28, 2009 (Dnr: 09-142M), with supplements on June 10, 2013 (Dnr: 2013-204-32M) and January 13 (Dnr: 2014-416-32) to approve studies of baseline characteristics and follow-up regarding new events among participants not included for randomization.
Results

Baseline characteristics of study participants

Table 3 shows baseline characteristics of analysed patients in papers I–IV. The mean age is lower in papers III and IV compared with paper II, reflecting that patients not fulfilling the inclusion criteria for the intervention trial where older with more comorbidity.

Table 3 - Baseline characteristics of the study populations in papers I–IV

<table>
<thead>
<tr>
<th>Paper</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>196765</td>
<td>1528</td>
<td>484</td>
<td>660</td>
</tr>
<tr>
<td>Age, mean</td>
<td>76.0</td>
<td>75.1</td>
<td>70.8</td>
<td>69.9</td>
</tr>
<tr>
<td>Female sex</td>
<td>98425 (50.0)</td>
<td>681 (44.6)</td>
<td>208 (43.0)</td>
<td>269 (40.8)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>52169 (27.4)</td>
<td>391 (25.6)</td>
<td>78 (16.1)</td>
<td>99 (15.0)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>30568 (20.5)</td>
<td>305 (20.0)</td>
<td>86 (17.8)</td>
<td>113 (17.1)</td>
</tr>
<tr>
<td>Smoking</td>
<td>21273 (16.2)</td>
<td>191 (12.7)</td>
<td>69 (14.3)</td>
<td>90 (13.6)</td>
</tr>
<tr>
<td>Index event</td>
<td>IS 196765 (100.0)</td>
<td>1083 (70.9)</td>
<td>289 (59.7)</td>
<td>387 (58.6)</td>
</tr>
<tr>
<td>TIA</td>
<td>0</td>
<td>445 (29.1)</td>
<td>176 (36.8)</td>
<td>250 (37.9)</td>
</tr>
<tr>
<td>ICH</td>
<td>0</td>
<td>0</td>
<td>17 (3.5)</td>
<td>23 (3.5)</td>
</tr>
<tr>
<td>Previous diagnosis of</td>
<td>Hypertension 56136 (55.5)</td>
<td>985 (64.5)</td>
<td>289 (59.7)</td>
<td>384 (58.2)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>24248 (12.3)</td>
<td>182 (11.9)</td>
<td>59 (12.2)</td>
<td>52 (7.9)</td>
</tr>
<tr>
<td>IS</td>
<td>28716 (14.6)</td>
<td>235 (15.4)</td>
<td>62 (12.8)</td>
<td>68 (10.3)</td>
</tr>
<tr>
<td>ICrH</td>
<td>3367 (1.7)</td>
<td>39 (2.6)</td>
<td>n/s</td>
<td>n/s</td>
</tr>
<tr>
<td>Treatment at discharge</td>
<td>Statins 41588 (43.1)</td>
<td>951 (62.2)</td>
<td>384 (79.3)</td>
<td>529 (80.2)</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>65825 (68.1)</td>
<td>1184 (77.5)</td>
<td>363 (75.0)</td>
<td>495 (75.0)</td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>109211 (75.8)</td>
<td>1233 (80.7)</td>
<td>390 (80.6)</td>
<td>529 (80.2)</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>16359 (11.4)</td>
<td>244 (16.0)</td>
<td>67 (13.8)</td>
<td>93 (14.1)</td>
</tr>
<tr>
<td>mRS 0–2</td>
<td>n/s</td>
<td>1002 (65.7)</td>
<td>419 (86.6)</td>
<td>598 (89.7)</td>
</tr>
</tbody>
</table>

Data presented as n (%) unless otherwise noted. IS indicates ischemic stroke; TIA, transient ischemic attack; ICH, intracerebral hemorrhage; ICrH, intracranial hemorrhage; and mRS, modified Rankin Scale.

In paper I, a reference population of 190,157 participants was developed. This group had a mean age of 75.8 years, 49.8% were women, and they had fewer comorbidities than patients with stroke: previous myocardial infarction, 7.7% versus 12.3%; previous IS, 3.6% versus 14.6%; and previous ICrH, 0.9% versus 1.7%.
Serious hemorrhage (papers I and II)

In paper I, a total of 196,765 patients diagnosed with an IS during 1998–2009 were followed in the first year after an ischemic stroke; in paper II, 1528 patients diagnosed with an IS or TIA during 2010–2013 were followed from discharge until 31 December 2015. The median observation time was 1099 days (interquartile range: 734–1556). Baseline characteristics of study populations in papers I and II are shown in Table 3 and Figure 2. The figure shows an increase in secondary prevention medication in the study population in the 2000s with a decreasing proportion of patients without any AT discharge and increasing proportion of patients with statins and antihypertensives.

![Figure 2 - Treatment at discharge in the study populations in papers I (2001–2009) and II (2010–2013) – proportions of the study population with antihypertensive treatment, statins, antiplatelet (AP), anticoagulant (AC), or no AP or AC treatment at discharge](image.png)
Incidence rate and cumulative incidence of ICrH

In paper I, a total of 3186 patients had a diagnosis of ICrH during the first year after an IS, 1932 within the first 30 days and 1254 during days 31–365. The incidence rate was 1.97% (95% CI: 1.91–2.03) per year at risk for the first year and 0.85% (95% CI: 0.81–0.89) excluding the first 30 days. In the NAILED population (paper II), the incidence rate of an ICrH after discharge, including traumatic ICrH, was 0.96% (95% CI: 0.71–1.28) per year at risk. The incidence rates of ICH after the acute phase were 0.59 (95% CI: 0.55–0.63) and 0.40% (95% CI: 0.25–0.62) per year at risk in papers I and II, respectively, and 0.04% (95% CI: 0.03–0.05) per year at risk in the reference population in paper I (see Table 4 for incidence rates).

### Table 4 - Incidence rates (% per year at risk) of intracranial hemorrhage (ICrH) and intracerebral hemorrhage (ICH) in paper I (days 31–365) and paper II (from discharge until end of study)

<table>
<thead>
<tr>
<th></th>
<th>Paper I</th>
<th>Paper II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICrH</td>
<td>ICH</td>
</tr>
<tr>
<td>All</td>
<td>0.85 (1254)</td>
<td>0.59 (874)</td>
</tr>
<tr>
<td>IS patients only</td>
<td>0.85 (1254)</td>
<td>0.59 (874)</td>
</tr>
<tr>
<td>Age at discharge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75 years</td>
<td>0.68 (495)</td>
<td>0.49 (362)</td>
</tr>
<tr>
<td>≥75 years</td>
<td>0.86 (759)</td>
<td>0.58 (512)</td>
</tr>
<tr>
<td>Treatment at discharge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>1.04 (144)</td>
<td>0.62 (94)</td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>0.75 (657)</td>
<td>0.47 (456)</td>
</tr>
<tr>
<td>Reference pop, study I</td>
<td>0.13 (231)</td>
<td>0.04 (74)</td>
</tr>
</tbody>
</table>

IS indicates ischemic stroke; ICrH, intracranial hemorrhage; and ICH, intracerebral hemorrhage

**Time-trends**

Between 1998 and 2009, the cumulative incidence of ICrH and ICH increased from 0.94%–1.21%, the first 30 days after an IS (p<0.001). The cumulative incidence decreased from 0.89%–0.72%, during days 31–365 (p=0.021), The cumulative incidence in the reference-population was between 0.10–0.13% during the study-period (Figure 3 and 4).

Incidence rate and cumulative incidence of serious hemorrhage

Of the 1528 patients in paper II, 125 had at least one new hospitalization with a hemorrhage diagnosed after discharge. Twelve of the hemorrhages were not considered serious according to our criteria. Thus, 113 (7.4%) had a serious hemorrhage: 45 ICrH, 41 GI, and 27 in other locations (flow chart, Figure 5). The median time to an event was 535 days (interquartile range: 209–942). The incidence rate of a serious haemorrhage after IS or TIA was 2.48% (95% CI: 2.05–2.97) per year at risk. Cumulative incidence of hemorrhage during the study period and incidence rates in different patient categories are shown in Tables 5 and 6.

Figure 5 - Study flow chart, paper II
Table 5 - Cumulative incidence of serious hemorrhage, intracranial hemorrhage (ICrH), gastrointestinal hemorrhage (GI), and other hemorrhages within 5 years after discharge from ischemic stroke or TIA (paper II).

<table>
<thead>
<tr>
<th>Years</th>
<th>All</th>
<th>ICrH</th>
<th>GI</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (N)</td>
<td>% (N)</td>
<td>% (N)</td>
<td>% (N)</td>
</tr>
<tr>
<td>1</td>
<td>3.08 (47)</td>
<td>0.85 (13)</td>
<td>1.11 (17)</td>
<td>1.11 (17)</td>
</tr>
<tr>
<td>2</td>
<td>4.66 (71)</td>
<td>1.64 (25)</td>
<td>1.71 (26)</td>
<td>1.31 (20)</td>
</tr>
<tr>
<td>3</td>
<td>6.56 (96)</td>
<td>2.62 (38)</td>
<td>2.32 (34)</td>
<td>1.62 (24)</td>
</tr>
<tr>
<td>4</td>
<td>7.64 (106)</td>
<td>3.07 (42)</td>
<td>2.85 (39)</td>
<td>1.72 (25)</td>
</tr>
<tr>
<td>5</td>
<td>8.50 (111)</td>
<td>3.59 (45)</td>
<td>3.02 (40)</td>
<td>1.89 (26)</td>
</tr>
</tbody>
</table>

Table 6 - Incidence rates of serious hemorrhage, ICrH, GI hemorrhage, and other hemorrhages within 5 years after discharge from IS or TIA in different patient groups (paper II).

<table>
<thead>
<tr>
<th>All</th>
<th>ICrH</th>
<th>GI</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>% per year at risk (N)</td>
<td>% per year at risk (N)</td>
<td>% per year at risk (N)</td>
<td>% per year at risk (N)</td>
</tr>
<tr>
<td>All</td>
<td>2.48 (113)</td>
<td>0.96 (45)</td>
<td>0.88 (41)</td>
</tr>
<tr>
<td><strong>Index event</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>2.72 (84)</td>
<td>1.07 (34)</td>
<td>0.94 (30)</td>
</tr>
<tr>
<td>TIA</td>
<td>1.98 (29)</td>
<td>0.74 (11)</td>
<td>0.74 (11)</td>
</tr>
<tr>
<td><strong>Antithrombotic treatment at discharge</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>2.74 (20)</td>
<td>1.20 (9)</td>
<td>1.07 (8)</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>2.37 (89)</td>
<td>0.93 (36)</td>
<td>0.78 (30)</td>
</tr>
<tr>
<td><strong>Functional level at discharge</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS 0–2</td>
<td>2.19 (74)</td>
<td>0.93 (32)</td>
<td>0.66 (23)</td>
</tr>
<tr>
<td>mRS 3–5</td>
<td>3.31 (39)</td>
<td>1.06 (13)</td>
<td>1.48 (18)</td>
</tr>
<tr>
<td><strong>Age at discharge</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75 years</td>
<td>1.70 (39)</td>
<td>0.64 (15)</td>
<td>0.64 (15)</td>
</tr>
<tr>
<td>≥75 years</td>
<td>3.26 (74)</td>
<td>1.28 (30)</td>
<td>1.11 (26)</td>
</tr>
</tbody>
</table>
**Mortality**

During the first year after admission, 22.3% and 13.4% (16.7% of IS patients) of patients died in papers I and II respectively. In paper II, 494 (32.3%) patients died during the entire follow-up (Figure 6). Among patients with a functional status of mRS 0–2 at discharge, the mortality in paper II was 4.2% in the first year and 18.4% during the follow-up. Corresponding numbers in the group with mRS 3–5 were 31.0% and 58.9%. The 30-day case fatality of a serious hemorrhage in paper II (all events) was 15.9%. The corresponding percentages were 12.2% for GI hemorrhages, 24.4% for ICrH, and 42.1% for ICH. In paper I, the 30-day case fatality values for non-traumatic ICrH and ICH were 31.5% and 35.5%, respectively. In paper II, a serious hemorrhage during follow-up was associated with higher 5-years mortality in the group with mRS 0–2 at discharge, compared to no hemorrhage (37.8% vs 16.8%, p<0.001). In the group with mRS 3–5, a hemorrhage had no effect on mortality (p=0.319; Figure 6).

![Figure 6](image_url)

**Figure 6** - Cumulative survival 5 years after discharge from hospitalization for ischemic stroke or transient ischemic attack. (A) All patients (n=1528, of whom 485 died). (B) Patients stratified by functional level at discharge (p<0.001). (C) Patients with mRS 0–2 at discharge, with or without a serious hemorrhage during follow-up (p<0.001). (D) Patients with mRS 3–5 at discharge, with or without a serious hemorrhage during follow-up (p=0.319); mRS: modified Rankin Scale.
Predictors of serious hemorrhage and ICrH

In paper I, male sex and a prior ICrH or ICH were associated with a new ICrH or ICH after an IS during both days 0–30 and days 31–365. Thrombolysis, atrial fibrillation and warfarin at admission were associated with an ICrH/ICH within 30 days. Age over 75 years was associated with a decreased risk of ICrH the first 30 days and an increased risk day 31-365. In paper II, a prior diagnosis of hypertension was associated with an increased risk of serious hemorrhage after an IS or TIA. AT at discharge was not associated with an increased risk of hemorrhage in papers I and II. For multivariable Cox regression analyses, see Tables 7, 8, and 9.

Table 7 - Multivariable logistic regression analysis of predictors of ICrH / ICH after IS, days 0–30.

<table>
<thead>
<tr>
<th></th>
<th>ICrH OR (95% CI)</th>
<th>p</th>
<th>ICH OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥75 years</td>
<td>0.82 (0.72–0.93)</td>
<td>0.002</td>
<td>0.84 (0.72–0.99)</td>
<td>0.033</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.82 (0.72–0.93)</td>
<td>0.002</td>
<td>0.78 (0.67–0.90)</td>
<td>0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.22 (1.06–1.40)</td>
<td>0.007</td>
<td>1.36 (1.15–1.61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Warfarin at admission</td>
<td>1.32 (1.03–1.69)</td>
<td>0.007</td>
<td>1.45 (1.09–1.93)</td>
<td>0.010</td>
</tr>
<tr>
<td>ICrH prior IS</td>
<td>7.54 (6.06–9.34)</td>
<td>&lt;0.001</td>
<td>5.29 (3.46–8.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>4.50 (3.72–5.44)</td>
<td>&lt;0.001</td>
<td>6.58 (5.37–8.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>0.86 (0.76–0.97)</td>
<td>0.015</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 8 - Multivariable Cox regression analysis of predictors of ICrH / ICH after IS, days 31–365.

<table>
<thead>
<tr>
<th></th>
<th>ICrH HR (95% CI)</th>
<th>p</th>
<th>ICH HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥75 years</td>
<td>1.25 (1.05–1.49)</td>
<td>0.012</td>
<td>1.15 (0.93–1.42)</td>
<td>0.197</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.74 (0.63–0.88)</td>
<td>0.001</td>
<td>0.76 (0.62–0.94)</td>
<td>0.010</td>
</tr>
<tr>
<td>ICrH prior IS</td>
<td>3.06 (2.05–4.56)</td>
<td>&lt;0.001</td>
<td>5.31 (3.11–9.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statins at discharge</td>
<td>0.81 (0.68–0.96)</td>
<td>0.015</td>
<td>0.71 (0.57–0.88)</td>
<td>0.001</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>0.47 (0.24–0.90)</td>
<td>0.024</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 9 - Multivariable Cox regression analysis of predictors of serious hemorrhage after IS or TIA.

<table>
<thead>
<tr>
<th></th>
<th>Serious hemorrhage HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥75 years</td>
<td>1.30 (0.85–1.99)</td>
<td>0.220</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.75 (0.52–1.09)</td>
<td>0.127</td>
</tr>
<tr>
<td>Prior hypertension</td>
<td>1.72 (1.10–2.68)</td>
<td>0.017</td>
</tr>
<tr>
<td>Statins at discharge</td>
<td>0.81 (0.55–1.20)</td>
<td>0.300</td>
</tr>
</tbody>
</table>
NAILED stroke trial (papers III and IV)

Figure 1 shows the flow of participants in papers III and IV. During the inclusion period between 1 January 2010 and 31 December 2013, a total of 871 participants were included. Of these, 537 were included until 30 June 2012 and compose the study population in paper III. In the 12-month follow-up (paper III), 53 participants (9.9%) discontinued, and in the 36-month follow-up (paper IV), 211 participants (24.2%) discontinued. Baseline data for all participants followed up in papers III and IV at 12 and 36 months are given in Table 11. Except for a borderline significant higher prevalence of diabetes in the control group, the groups were well balanced in terms of baseline characteristics at follow-up. The participants who did not complete the 12- and 36-month follow-up periods were older and had more co-morbidities. In paper III, the numbers of BP and LDL-C measurements were fairly equal between the control and intervention groups, including the measurement in the trial, between 1 and 12 months. Table 10 shows the numbers of participants screened and randomized, reasons for exclusion, numbers at last follow-up, and reasons for discontinuation. In total, 99 participants died during the 36 months of follow-up, 55 in the intervention and 44 in the control group. The intervention and control groups did not differ significantly in terms of proportion of cardiovascular or all-cause mortality (p=0.51 and 0.24, respectively).

Table 10 - Flow of participants in papers III and IV – Numbers of participants, screened, randomized, and followed up and reasons for being lost to final follow-up

<table>
<thead>
<tr>
<th></th>
<th>12 months follow-up</th>
<th>36 months follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Paper III</td>
<td>Paper IV</td>
</tr>
<tr>
<td>Screening</td>
<td>N=1102</td>
<td>N=1776</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>N=90</td>
<td>N=130</td>
</tr>
<tr>
<td>Excluded</td>
<td>N=356</td>
<td>N=548</td>
</tr>
<tr>
<td>Declined to participate</td>
<td>N=119</td>
<td>N=225</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td>N=2</td>
</tr>
<tr>
<td>Randomization</td>
<td>N=537</td>
<td>N=871</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Intervenation</th>
<th>Control</th>
<th>Intervenation</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died</td>
<td>266</td>
<td>271</td>
<td>433</td>
<td>438</td>
</tr>
<tr>
<td>Active withdrawal</td>
<td>9</td>
<td>9</td>
<td>40</td>
<td>31</td>
</tr>
<tr>
<td>Unable to continue</td>
<td>15</td>
<td>16</td>
<td>46</td>
<td>34</td>
</tr>
<tr>
<td>No measurement</td>
<td>0</td>
<td>3</td>
<td>25</td>
<td>29</td>
</tr>
<tr>
<td>12/36 m follow-up</td>
<td>241</td>
<td>243</td>
<td>320</td>
<td>340</td>
</tr>
</tbody>
</table>
Table 11 - Baseline characteristics of all participants randomized 2010–2013 and of participants at 12 and 36 months of follow-up in papers III and IV

<table>
<thead>
<tr>
<th></th>
<th>12-month follow-up, paper III</th>
<th>36-month follow-up, paper IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention</td>
<td>Control</td>
</tr>
<tr>
<td>N</td>
<td>241</td>
<td>243</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>71.5</td>
<td>70.1</td>
</tr>
<tr>
<td>Women</td>
<td>104 (43.2)</td>
<td>104 (42.8)</td>
</tr>
<tr>
<td>Qualifying event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>143 (59.3)</td>
<td>146 (60.1)</td>
</tr>
<tr>
<td>Intracerebral hematoma</td>
<td>9 (3.7)</td>
<td>8 (3.3)</td>
</tr>
<tr>
<td>TIA</td>
<td>89 (36.9)</td>
<td>89 (36.6)</td>
</tr>
<tr>
<td>mRS 3–5</td>
<td>38 (16.2)</td>
<td>27 (11.1)</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>41 (17.0)</td>
<td>32 (13.2)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>30 (12.4)</td>
<td>29 (11.9)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>10 (4.1)</td>
<td>7 (2.9)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>39 (16.2)</td>
<td>39 (16.0)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>40 (16.6)</td>
<td>46 (18.9)</td>
</tr>
<tr>
<td>Smoker</td>
<td>28 (11.6)</td>
<td>41 (16.9)</td>
</tr>
<tr>
<td>Medication at 1 month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive drug</td>
<td>177 (73.4)</td>
<td>186 (76.5)</td>
</tr>
<tr>
<td>Statin</td>
<td>191 (79.3)</td>
<td>193 (79.4)</td>
</tr>
<tr>
<td>Antiplatelet drug</td>
<td>191 (79.3)</td>
<td>199 (81.9)</td>
</tr>
<tr>
<td>Anticoagulant drug</td>
<td>36 (14.9)</td>
<td>31 (12.8)</td>
</tr>
<tr>
<td>Health care contacts 1–12 m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contact with primary care centre</td>
<td>234 (97.1)</td>
<td>231 (95.1)</td>
</tr>
<tr>
<td>No. of BP and/or LDL-C evaluations, median (iqr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary care centre</td>
<td>1.0 (0.0–2.0)</td>
<td>3.0 (1.0–4.0)</td>
</tr>
<tr>
<td>Within NAILED stroke trial</td>
<td>2.0 (1.0–3.0)</td>
<td></td>
</tr>
</tbody>
</table>

Data presented as n (%) unless otherwise noted. There were no significant differences between the intervention and control groups for any of the variables presented in the table except for diabetes in paper IV, 36 months follow-up, p=0.049.
Mean BP, LDL-C, and proportions reaching treatment target

The systolic BP (SBP) values at 12 and 36 months were 3.3 (95% CI: 0.3–6.3) and 6.1 mmHg (95% CI: 3.6–8.6) lower in the intervention compared with the control group. For diastolic (DBP), the corresponding numbers were 2.3 (95% CI: 0.5–4.2) and 3.4 mmHg (95% CI: 1.8–5.1), and for LDL-C, they were 0.3 (95% CI: 0.1–0.4) and 0.3 mmol/L (95% CI: 0.2–0.5) lower. Mean BP, LDL-C, and difference between intervention and control group at 36 months are shown in table 12.

An interaction analysis on the 12-month measurement in paper III is shown in Figure 7 A-C. It shows a significant interaction effect between group allocation (intervention vs control) and baseline values for BP/LDL-C (reaching or not reaching treatment target), SBP (p=0.001), and LDL-C (p<0.001). The adjusted SBP and LDL-C in the intervention group with baseline measurement above treatment target was 8.0 mmHg (95% CI: 4.0–12.1) and 0.6 mmol/L (95% CI: 0.4–0.9) lower than in the control group, respectively. The corresponding difference in SBP at 36 months was 9.2 mmHg (95% CI: 5.6–12.8) favouring the intervention group after decrease in SBP of 20.9 mmHg (95% CI: 17.9 – 23.9), down to 130.8 mmHg (95% CI: 128.2 – 133.4) over the study period.

Figure 7 shows the proportions reaching treatment target at 12 months follow-up in paper III and the proportion that changed from over treatment target at 1 month to below target at 12 months follow-up. The difference in proportion reaching treatment target were significant for SBP (p=0.008) and LDL-C (p<0.001) at 12 months (paper III, figure 7 D-F) and for SBP, DBP and LDL-C (p<0.001 for all) at 36 months (paper IV, table 12 and figure 9).

Time trends

The difference in proportion reaching treatment target as well as the difference in mean value between the two groups increased during the whole study period for SBP and DBP. For LDL-C, the difference seen at the 12-month follow-up in paper IV remained unchanged at 24 and 36 months (Figure 8 and 9). Figure 10 shows the number of follow-ups with a measurement above treatment target for SBP, DBP, and LDL-C. It shows that 20%–30% were within treatment target at all follow-ups (0) for SBP and LDL-C in both groups, but that almost no participants in the intervention group had no measurement within target (4) for SBP, DBP, and LDL-C. At 36 months, 44.1% in the intervention group and 72.9% in the control group (p<0.001) had at least one measurement above target. During the whole study period, only 5.9% and 4.7% (p=0.493) of the participants in the two groups reached treatment target values at all measurements for SBP, DBP, and LDL-C.
Figure 7 – Analyses at 12-months follow up (paper III). A-C: Effect of the interaction between group allocation and the baseline level of BP or LDL-C level on the 12-month adjusted mean (A) SBP (p=0.001), (B) DBP (p=0.054), and (C) LDL-C (p<0.001) values. D-F: Proportion of participants below treatment target at 1 and 12 months. The lightly shaded portion of each 12-month stack represents the proportion whose values changed from above to below target between 1- and 12-months follow-up.
Table 12 – Outcome at 36 months. Unadjusted mean value at 1 and 36 months, difference between 1 and 36 months, adjusted mean value at 36 months, in-between group difference and proportion within group reaching treatment target.

<table>
<thead>
<tr>
<th></th>
<th>SBP mean, mmHg (95% CI)</th>
<th>DBP mean, mmHg (95% CI)</th>
<th>LDL-C mean, mmol/L (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention</td>
<td>Control</td>
<td>Intervention</td>
</tr>
<tr>
<td>Unadjusted 1m</td>
<td>136.9 (135.0-138.7)</td>
<td>137.2 (135.3-139.2)</td>
<td>80.8 (79.5-82.1)</td>
</tr>
<tr>
<td>Unadjusted 36 m</td>
<td>128.8 (127.1-130.5)</td>
<td>134.9 (133.1-136.8)</td>
<td>76.4 (75.3-77.6)</td>
</tr>
<tr>
<td>Diff</td>
<td>8.1 (5.8-10.3)</td>
<td>2.3 (0.1-4.4)</td>
<td>4.4 (2.9-5.8)</td>
</tr>
<tr>
<td>Adjusted 36 m</td>
<td>128.1 (125.8-130.5)</td>
<td>134.2 (131.8-136.6)</td>
<td>75.3 (73.8-76.9)</td>
</tr>
<tr>
<td>Adjusted difference interv vs control</td>
<td>6.1 (3.6-8.6), p&lt;0.001</td>
<td>3.4 (1.8-5.1), p&lt;0.001</td>
<td>0.3 (0.2-0.5), p&lt;0.001</td>
</tr>
<tr>
<td>Treatment target 36 m, yes (%)</td>
<td>79.4</td>
<td>55.3</td>
<td>90.3</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

Figure 8 Unadjusted mean values for SBP, DBP, and LDL-C at 1, 12, and 24 months before and after medication titration and at 36 months.
Discussion

Methodological considerations

The studies presented in this thesis were hospital-based cohort studies (papers I and II) and results from the RCT NAILED stroke trial (papers III and IV). Paper I was based on registered data from Riksstroke. Paper II was based on data from the screening phase of the NAILED stroke trial, and papers III and IV on data from the NAILED intervention phase. Possible methodological issues within these papers, such as information bias, missing data, confounding, and selection bias, are discussed below.

Information bias

The use of registers with large number of patients, as in paper I, enables precise estimates, even in subsets of patients and in outcomes involving approximately 1% of the study population, as with ICrH in an IS population. The observations in these studies complement the RCTs and can help reveal outcomes in patient groups not otherwise represented in the randomized trials. However, register studies have their weakness and depend on the quality of the data used. The IPR has high PPV and sensitivity for first-time stroke events but is lower in recurrent events. No specific validation is available for ICrH or ICH, but the incidence rates for ICH in IS patients in papers I and II are similar. In addition, the rate of ICH in the reference population in paper I is similar to the incidence in a non-stroke population in previous studies, suggesting fairly reliable results for ICH. With decreasing PPV in recurrent events in IPR, there is a risk of overestimation of ICrH in patients with an ICrH prior to the IS in paper I. However, any overestimation should be constant over time and not alter the result on time trends.

The CDR comprises data on cause of death. The information from the register is completed by a physician. It has been validated, and together with the NPR, it has a high PPV and sensitivity for capturing stroke events, especially for first-ever stroke, when compared with stroke registers. However, when used alone, CDR has a PPV of 62% for all stroke, not discriminating IS from ICH, and the PPV decreases in patients who are not hospitalized. Another study shows that CDR alone has an all-stroke specificity of 68%. In the database, we have information from the CDR, but because the diagnosis of an ICH or ICrH compared with any stroke or other cause of death outside the hospital without a certain diagnostic work-up was too uncertain, we did not include these events in the analysis. With inclusion of patients with an ICrH as a major cause of death in the CDR without a diagnosis in the IPR, the ICrH incidence rate during days 31–365 days after IS was 0.93% (n=1368) per year at risk instead of 0.85% (n=1254).
The incidence in paper I might be underestimated, but the slightly higher incidence do not change any conclusions.

Data on medication in papers I and II have to be interpreted carefully because the information is from discharge without numbers on persistence. The use of data from the Swedish Prescribed Drug Register, which holds information on all prescriptions dispensed to Swedish patients, could have increased the accuracy of and knowledge about treatment at the time of the event in papers I and II, but these data was not part of our analysis.

In papers I and II, there are some differences in which ICD-10 codes are used for defining ICrH. In paper I, as prespecified, we investigated diagnoses of non-traumatic ICrH and ICH. The cause of some ICrH, especially subdural hematoma, might be difficult to determine regarding trauma or not. In paper I, we could not validate the diagnoses from IPR, which carries a risk of either over- or underestimating non-traumatic ICrH. Therefore, we included all diagnosis of ICrH in paper II. However, the use of the ICH diagnosis (ICD-61) should be comparable in papers I and II so that in this thesis, results for ICH and ICrH are both reported.

The definitions of a serious hemorrhage in RCTs are heterogeneous and rates of hemorrhage difficult to compare among trials\textsuperscript{127-130}. Many definitions also require knowledge about changes in hemoglobin values. In paper II, the last hemoglobin value before admission could be more than 2 years old, precluding any use of these definitions. Instead, we searched for both primary and secondary diagnoses of hemorrhages as in other observational trials\textsuperscript{70, 74, 131}. We evaluated these diagnoses by scrutinizing patient records to assess their correctness and used both primary and secondary diagnoses if they met our criteria. The possibility of validating the diagnosis should increase the internal validity. The severity of GI and other hemorrhages might range from mild to life-threatening. We included only hospitalized cases in our definition of serious hemorrhages. Thus, incidence rates of all GI and other hemorrhages might be underestimated.

In papers III and IV, measurement of BP and LDL-C was conducted at each participant’s closest health station by the local staff. The participant brought instructions. However, many health workers and health stations were involved in the measurements, leaving a possibility for measurement error or equipment issues. These potential errors should, however, be randomly distributed among the participants and randomized groups and should not affect between-group comparisons.

The NAILED stroke trial was an open trial. There was no blinding of the groups, so both participants and staff were aware of allocation. The protocol and the
nature of the intervention made blinding impossible. This factor could, of course, affect the results of the study. The measurement values in the control group were forwarded by the study team to each participant’s GP without any further actions or instructions. We cannot exclude that this step led to measurements that would not otherwise have been conducted, greater awareness by the patient, and more adjustments and control of the risk factors by the GP than would have otherwise been the case. If so, a decrease in differences between the groups and underestimation of the intervention’s effects are possible.

**Missing data**

In paper I, data were missing for variables included in the Cox PH regression analysis in 1%–6% of cases. Smoking was omitted from the analysis because of missing data in 13% of cases. In paper II, data were missing in less than 2% of any variable in the univariable analysis and in only single cases in the multivariable analysis. Complete cases were used in all analyses. In papers III and IV, participants were lost to follow-up for three main reasons: death, unable to continue because of severe disease, or active withdrawal; thus, these were not complete cases. Fifty-three and 211 participants did not complete the 12 and 36 months of follow-up, respectively.

In statistical analysis, imputation is a possible process to adjust for a potential systematic bias of the missing data. However, imputation still requires invented values. With small proportions of missing data in papers I and II, and thereby low risk that it would affect the results, we chose not to impute values.

In papers III and IV, last value carried forward could have been a possible solution to handle missing follow-up measurements. The main reasons for participants being lost to follow-up were natural causes, reflecting the clinical reality of this stroke/TIA population and we therefore chose not to impute values. The participants lost to follow-up were older with more comorbidities, but the distribution of baseline characteristics remained similar between the groups. In addition, there were no significant between-group differences in mortality, including cardiovascular deaths.

**Confounding**

Confounders are factors that affect both an exposure and the outcome, thus producing all or part of an effect. The multivariable analysis in the Cox regression model is one way to handle possible confounders. Still, we can try to adjust only for the known variables. In non-randomized observational studies such as papers I and II, there certainly are unknown confounders for which we cannot adjust.
In investigations of different treatments, confounding by indication is a risk. In papers I and II, we found no significant association between AP and AC treatment and serious hemorrhages, except for warfarin at admission for ICrH days 0–30 in paper I. We do not know the reason for decisions on discharge treatment, but the risk of hemorrhage and severe disease is a probable cause to abstain in many cases. Therefore, associations from these analyses in observational studies should not lead to any conclusions regarding causality.

**Selection bias, coverage, and generalizability**

Riksstroke had a coverage of approximately 80%–90% during the years included in paper I. The coverage increased over time, especially during the first years. The lower coverage in the first years could be a result of selective registration, which would decrease the internal validity of paper I. On the other hand, mean age and the proportions of men and women were similar during the years studied with little variation in 1-year mortality, indicating that the different time-cohorts in paper I should be comparable. Patients at risk of not being included in Riksstroke are those who die early, are not treated at a stroke unit, or receive care in a nursing home.

In paper II, all patients treated for a stroke or TIA at Östersund hospital were included. The case-finding methods in the NAILED stroke trial were validated against set diagnoses prior to the start of inclusion, and no missed cases of patients with a discharge code of stroke or TIA were found. Studies report that 84%–92% of all stroke patients are treated in-hospital. Patients more likely to not be treated in the hospital are institutionalized patients, those with very mild symptoms, or those who die outside of the hospital.

Thus, there is a selection bias at inclusion in papers I and II, and patients with stroke or TIA not admitted to hospital are not included. As hospital-based cohort studies, however, the internal validity must be considered high. The inclusion was not restricted by age, functional status, or co-morbidity in this otherwise unselected cohort. The results should be generalizable to other hospital-treated cohorts in Sweden and to other countries with similar demographics and stroke epidemiology.

Within the NAILED stroke trial, an analysis of which patients were eligible or considered unable to participate in a telephone-based follow-up showed that 35.7% of stroke and TIA patients could not participate, mainly because of physical or cognitive disability. Age >85 years, impaired functional status with mRS >3, and lower educational level were associated with increased risk of exclusion. Exclusion also was associated with a 12-fold greater risk of death within the first year, similar to mortality in patients with mRS 3–5 in paper II. The determination
of eligibility or not at discharge might, however, have excluded patients who with a few weeks of rehabilitation could have been suited for the intervention. Also, a strategy that would fit patients with aphasia or hearing problems who now had to be excluded could have made inclusion of this ~7% of the patient group possible. Thus, a higher proportion of the stroke population might have been eligible for the NAILED intervention. Nevertheless, with the estimated inability to participate in the intervention as the only exclusion criterion, with a screening process with all patients admitted to Östersund hospital during 4 years considered for participation, the results with this study population must be considered generalizable to similar settings.

In paper III and IV, differences in strategy of risk factor follow-up between the intervention and “usual care”, i.e. the control group, resulted in differences in outcome. Consequently, generalizability of the result will depend mainly on whether the achievements of “usual care” in our population can be considered representable of “usual care” in other populations. Compared to the NAILED control group, the proportions reaching treatment targets has been similar or lower in observational studies from Sweden\textsuperscript{97} and internationally\textsuperscript{93-96}, indicating that the results from the NAILED stroke trial should be reproducible in other populations.

**General discussion**

**Serious hemorrhages**

*Incidence rate of ICrH*

The risk of an ICrH after the acute phase was 0.9%–1.1%, depending on the definition of ICrH in papers I and II. For ICh after IS, the risk was 0.4%–0.6% per year at risk in papers I and II and 0.04% in the reference population in paper I. The incidence rates of ICh in patients discharged with AP (0.4%–0.5%), was comparable with rates in the clopidogrel arm in the PROFESS study\textsuperscript{52} and higher than in the ASA arm in the SPS3 study\textsuperscript{54}. The ICh rates in patients discharged with warfarin are comparable with the warfarin arm in IS and TIA patients included in studies of the NOACs rivaroxaban\textsuperscript{63} and dabigatran\textsuperscript{61}. In the trial on apixaban, the incidence of ICh was, however, higher than in our populations\textsuperscript{62}.

*Incidence rate of all serious hemorrhage*

The risk of a serious hemorrhage in paper II was 2.5% per year at risk, 2.7% in patients discharged with AC treatment, and 2.4% in those discharged with AP. These rates are comparable with those in a Swedish Riksstroke-based study in patients with IS, 2001–2005\textsuperscript{74}. They also are comparable with rates of serious hemorrhages in AC-treated patients in a meta-analysis of RCTs of warfarin and
AP-treated stroke patients with a definition of major hemorrhage similar to ours. However, they are more than double the risk of AP-treated patients in that meta-analysis.\textsuperscript{70}

Factors associated with an increased risk of hemorrhage
Thus, the incidence rates of ICH is 15 times higher after IS compared to the reference group in paper I. The rate of ICH in the IS population was roughly similar to rates in RCTs. For all serious hemorrhage incidence rates are comparable to rates in RCTs for AC, but higher for AP than in the RCTs.

Three mechanisms that can explain the increased risk of hemorrhage in IS and TIA patients are 1) Most IS and TIA patients are discharged with AT, associated with increased risk of hemorrhage. 2) Risk factors associated with vascular disease including ischemic stroke also increase the risk of hemorrhage. These factors include age, diabetes, hypertension, smoking and male sex.\textsuperscript{23-26} The prevalence of these risk factors are high in the study population in papers I and II. 3) The risk of hemorrhage seems to be higher in patients with manifest vascular disease than in patients with risk factors only, and particularly so in stroke patients. In RCTs patients with stroke had higher risk of ICrH compared with other patients with other cardiovascular diseases.\textsuperscript{65, 135, 136}

In papers I and II the study populations were older and had more comorbidities compared with many RCTs. Higher prevalence of factors known to be associated with an increased risk of hemorrhagic events probably contributed to the higher incidence of serious hemorrhage in AP treated patients in paper II compared with AP RCTs. Consequently, we found higher incidence rates in older patients and patients with impaired functional status at discharge - two groups sparsely represented in clinical trials. The incidence rates was almost twice those of patients over compared to under age 75 years. An increased risk of hemorrhage in elderly is also observed in Åsberg et al and Li et al and is driven by an increase of upper GI hemorrhage.\textsuperscript{74-76} With a mean age of 75 years in paper II compared with 59-70 in the AP RCTs the increase in GI hemorrhages could explain some of the higher hemorrhage rates in our study.

In RCTs of recommended AT the benefit of decreased risk of new ischemic events outweighs the risk of a hemorrhage. Also, the cumulative incidence of serious hemorrhage observed in paper II (3.1% in 1 year and 8.5% in 5 years) is considerably lower than the risk of a new IS (11% and 26%) in meta-analysis of observational studies on the risk of recurrent IS.\textsuperscript{37} However, in papers I and II, more than 40% of the patients were over 80 years age, representing patients who are not included in the RCTs. With the increased rate of hemorrhage in elderly, the question is if the risk–benefit ratio seen in RCTs is applicable to this population.
For AC treatment, many models are available to estimate the risk of embolic ischemic events\textsuperscript{137} and hemorrhage\textsuperscript{138}. Here, observational studies show that most patients with AF seem to benefit from AC treatment, and that with an increased risk of hemorrhage, the risk of embolic events increases even more\textsuperscript{139}. A recent study shows an increased use of AC, especially among elderly, with a decreased rate of IS but an unchanged rate of serious hemorrhage\textsuperscript{140}. In a RCT with a mean age of 82 years, including a small subgroup with IS and TIA patients, AC seems beneficial also in elderly compared with AP\textsuperscript{141}.

S2TOP-BLEED\textsuperscript{142} represents one attempt to develop a prediction model for major bleeding in IS and TIA patients on AP. The model includes factors associated with increased risk of hemorrhage in papers I and II, such as impaired functional status, hypertension, prior hemorrhage or stroke, and male sex. In a validation of the scale, the authors could confirm that the risk of hemorrhage was associated with risk of new ischemic events, and despite diminishing, the benefit outweighed the risk\textsuperscript{143}. In contrast, Li et al found that in patients aged >85 years, the risks and benefits of AP could possibly be equal\textsuperscript{76}. In a recent study on data from all RCTs on ASA, Rothwell et al reported on data from all randomized trials on ASA that the main effect comes within the first weeks and that all ages benefit from it, but that there is no certain effect after 12 weeks\textsuperscript{144}. The result from this study, together with the aforementioned observational studies raise the question of what the tipping point is at which risk outweighs benefit and what the timing for withdrawal in older and fragile patients should be, if any. More studies are needed.

Some steps are possible to reduce serious hemorrhage. In short-term use, proton pump inhibitors (PPI) could reduce the risk of upper GI hemorrhage with 70\textendash{}90\%\textsuperscript{145} and the numbers needed to treat to prevent an upper GI hemorrhage decrease markedly with age\textsuperscript{76}, but more studies on risks and benefits of long-term use of PPI are needed.

Also, better BP control could reduce the risk of serious hemorrhage. Hypertension is a risk factor for serious hemorrhage in IS and TIA patients\textsuperscript{135, 142, 146, 147} and in the multivariable analysis in paper II, a diagnosis of hypertension prior to IS or TIA was associated with an increased risk of serious hemorrhage. Hypertension is common: approximately 60\% in papers I and II had a diagnosis of hypertension prior to their stroke or TIA, and 68\%\textendash{}78\% were discharged with antihypertensive treatment. Improved BP control is important to reduce the risk of ICrH\textsuperscript{147}. A BP $>140$ mmHg increases the risk of ICH after IS\textsuperscript{148\textendash{}150} as well as of recurrent ICH\textsuperscript{151}. Still, many patients do not reach the treatment target\textsuperscript{93\textendash{}97}, and measurements to improve BP control are further discussed below.
In paper I, prior ICrH/ICH is strongly associated with a new ICrH/ICH after IS. Patients with prior ICH are at increased risk of new events, both IS and ICH\textsuperscript{39,44}, complicating decisions about AT treatment and the risk–benefit assessment. Observational studies suggests that restart of AC might be beneficial\textsuperscript{152-155}, while the risk–benefit ratio is more uncertain in restarting AP\textsuperscript{153,156} in observational studies. The results of ongoing RCTs are needed that assess the risk–benefit of restarting AC\textsuperscript{157} and AP\textsuperscript{158} in patients with ICH.

Interestingly, AT was not associated with an increased risk of serious hemorrhage or ICrH in the multivariable Cox regression analyses. Also, in contrast to the higher incidence of ICH the intervention group in the SPARCL trial\textsuperscript{83} we found no association of statins with increased risk of hemorrhage in papers I and II but rather an association with a decreased risk of ICrH/ICH. However, we know only the medication on discharge and nothing about its use during the follow-up. There is also, of course, a risk of selection bias, and because ours is an observational study, we cannot draw conclusions on causality.

\textit{Time trends}

In paper I, there is a decrease in ICrH day 31-365, despite an increased proportion of patients being discharged with AT the same period. Although we only can speculate, there is also a trend to a larger proportion being discharged with antihypertensives that might have contributed to the decrease in ICrH in the same period.

In paper I, during the 2000s, there was an increase of ICrH in the acute phase. This increase coincided with the introduction of thrombolysis, which is strongly associated with ICrH in the multivariable analysis in paper I. Patients over age 75 years are represented in RCTs on thrombolysis. Thrombolysis has been analysed in both RCTs and observational studies, and the benefit outweighs the known risk of ICrH, including in older patients\textsuperscript{159,160}.

\textit{Mortality}

ICrH is the most feared hemorrhagic complication\textsuperscript{75}. In papers I and II, the 30-day fatality rates of ICrH, ICH, and GI hemorrhage were 24%–32%, 36%–42%, and 12%, similar to those described in previous studies\textsuperscript{19,34,74}. In the group with mRS 0–2, 8 of 11 of patients with a hemorrhage who died within 30 days had a ICrH. A serious hemorrhage decreased the chance of 5-year survival in patients with mRS 0–2. In the group with mRS 3–5 at discharge, a serious hemorrhage did not affect survival at the group level, probably because of the high mortality, with 31% dead within the first year after discharge compared with 4.2% in patients with mRS 0–2. With the high mortality in the group with mRS 3–5, it is uncertain if secondary prevention might improve survival. On the other hand, the rates might have been even higher without secondary prevention.
NAILED

Papers III and IV showed that the nurse-led, telephone-based follow-up including medication titration was more efficient than usual care in improving BP and LDL-C levels and proportions reaching treatment target. The effect was significant at 12 months, and for BP, the effect increased with time. At 36 months, the difference between groups was 6.1/3.4 mmHg. Paper III showed that the effect was derived from the intervention with an interaction between group allocation and baseline values for both SBP and LDL-C; there were no significant differences between groups for participants already below treatment target at baseline. Among participants above target at baseline for SBP in paper III, the difference between the groups was 8.0 mmHg. In patients above target for SBP at baseline in the intervention group in paper IV, the SBP decreased by 20.9 mmHg, down to 130.8 mmHg at 36 months. Patients above target in the control group had a decrease to 140.0 mmHg, a difference between the groups of 9.2 mmHg. This outcome could be compared with the PROGRESS trial that showed a 9/4 mmHg lower BP in the intervention group compared with the control group, that rendered a RRR for a new stroke of 28%.

Many efforts have targeted finding strategies to improve modifiable risk factors in patients after stroke. A recent update of the Cochrane review, “Interventions for improving modifiable risk factor control in the secondary prevention of stroke”, including results from paper III in this thesis, states that educational interventions alone seem to have no effect but that organizational interventions (including the NAILED stroke trial) might be associated with an improvement in achieving BP targets. The interventions studied, however, are heterogeneous in design, outcomes, and duration. There is, for example, significant heterogeneity in the pooled results on BP in studies with organizational interventions. Dissection of the interventions in attempt to identify key components are not uncomplicated, but could improve conclusions about what seems to be successful. Four components characterizing the NAILED stroke trial are that it 1) was telephone-based), 2) was nurse-led, 3) offered the possibility of medicine titration, and 4) had a follow-up period of 3 years (paper IV). These components are discussed below.

Several studies have used telephone partly or completely in an intervention, including some with promising results on BP, as in papers III and IV, demonstrating its feasibility. Telephone-based follow-up can be useful for several reasons. It can be a low-resource tool, facilitate a hospital-based follow-up in regions where many patients live far from the hospital, and facilitate follow-up for patients with a low functional level.
Primary contact with a nurse instead of a physician is also a possible resource-saving alternative. Several studies that have assessed nurse-led follow-up have indicated success\textsuperscript{104,161,163}, but as with other interventions, they vary in design and method, so distinguishing the useful elements might be complex. However, the combination of a nurse-led intervention with the possibility of adjusting medication within the trial\textsuperscript{105,108,163,164}, instead of recommending that the patient seek or be referred to the GP \textsuperscript{97,101,106}, seems to be positive.

We see in paper IV that most of the participants have the possibility of reaching the treatment target. The proportions of the intervention and control groups reaching their targets are quite different, with almost none in the intervention group with measurement above target in all four follow-ups. The strict study protocol instructs the study nurse to contact the study physician when a treatment target is not reached. In addition, the study physician must adjust the medical treatment as long as there is no medical contraindication. These factors might help explain the effect seen in the intervention group. The instruction to always act on measurements above treatment target minimizes therapeutic inertia, defined as: “providers’ failure to increase therapy when treatment goals are unmet”\textsuperscript{165}. Factors associated with this inertia include the primary care setting, male sex, older age, SBP and/or DBP values close to normal and treatment with more than one antihypertensive drug\textsuperscript{166}. Several of these factors could be applied to participants in the control group.

Paper IV shows that between titration and next follow-up, some participants go from under to above treatment target and some patients not in need of titration at one follow-up will need it the next. This change might be explained by one of several reasons, including 1) measurement errors (discussed above), 2) lack of persistence, and 3) BP variability.

Persistence declines soon after a stroke\textsuperscript{91,92}. In studies on BP, it is often various and low for antihypertensive and lipid-lowering treatments\textsuperscript{167-172}. Lack of persistence is also associated with increased risk of recurrent stroke\textsuperscript{170,171}. Factors associated with decreased persistence include beliefs about the treatment, the necessity for the treatment, potential side-effects, and fear of over prescription. Support of next of-kin, institutional living, or a scheduled follow-up are associated with improved adherence in previous studies\textsuperscript{91,92,172-176}.

The NAILED intervention included opportunity for the patient of discussing risks and benefits and understanding the indication for treatment might address some of the factors associated with lack of persistence. However, most interventions to improve persistence in a stroke/TIA population have failed to show positive results alone but might be beneficial together with other elements of follow-up\textsuperscript{161}. The trend during the follow-up was that the proportion reaching treatment target
increased for BP but remained the same for LDL-C after 12 months. Lack of persistence to statins could be one explanation, but persistence within NAILED has not yet been analysed, so no further conclusions can be drawn.

BP variability is well described in a stroke TIA population\textsuperscript{177}, is reproducible\textsuperscript{178}, and increases the risk of stroke\textsuperscript{179}. Due to visit-to-visit variability, measuring BP on one occasion each year might be insufficient to capture all patients who could benefit from adjusted hypertensive treatment, and continued follow-up is needed also in participants below treatment target. For practical reasons and to reflect the clinical setting of usual follow-up, the BP measurements were taken at one visit in the nearest health-station. Ambulatory measurement or home measurement could be a way to capture more patients at risk\textsuperscript{106} but is outside the frame of the NAILED stroke trial and would need a different and possibly more resource-demanding set-up.

In paper IV, the follow-up period was at 36 months. Few studies on intervention of modifiable risk factors after stroke or TIA have had follow-up beyond 12 months\textsuperscript{99, 110, 180}, and only one implemented intervention\textsuperscript{99} after 12 months. None of these trials with long-time follow-up have shown any significant effect on risk factor levels. In that sense the NAILED trial make a unique contribution. We showed that positive results with the intervention both during short-term and long-term follow-up and that the difference in mean BP and proportion reaching BP target increased over time. Only about 5\% of participants in both the intervention and control groups had BP and LDL-C values within target at all follow-ups. This indicates that patients benefit from continuous follow-up, which is true for all patients, not only those who have values above treatment target at baseline.
Conclusions

- The risk of an ICrH was 1.97% per year at risk, within the first year after IS, 0.85% excluding the first 30 days.

- From 1998 to 2009, the cumulative incidence of ICrH/ICH increased the first 30 days after IS. The cumulative incidence decreased day 31–365 after IS, despite an increased use of AT.

- The risk of a serious bleeding was 2.5% per year at risk, after discharge from an IS or TIA. The incidence of serious hemorrhage in patients discharged with AP was higher than in RCTs.

- Fragile patients such as the elderly and/or those with impaired functional status have higher incidence rates of hemorrhage. This together with a very high mortality makes secondary prevention challenging in these patients.

- A serious hemorrhage seems to increase the risk of mortality in patients with no or slight disability but not in patients with impaired functional status.

- Male sex and prior ICrH/ICH are associated with increased risk of ICrH/ICH after IS, and a prior diagnosis of hypertension is associated with a higher risk of all serious hemorrhages.

- The nurse-led, telephone-based intervention including titration of medication used in the NAILED stroke trial improved BP and LDL-C levels with larger proportions reaching treatment targets, both during short- and long-term follow-up.

- The effect of the NAILED trial intervention increased over time. There is a need for continuous, long-term follow-up to maintain control of risk factors after stroke and TIA.
Future perspectives

In Sweden, incidence rates of stroke are declining, and mortality after a stroke is decreasing. However, the population is aging, and with less case fatality, the number of stroke survivors will increase. These patients have a high risk of new vascular events and need the best possible secondary prevention.

This thesis shows that a more active follow-up of patients after stroke or TIA is needed to improve secondary prevention.

More survivors result in a patient cohort with older average age and more comorbidities, a group that is usually underrepresented in RCTs. In these patients, with other risk profiles and prognosis, observational studies such as papers I and II are important because they complement RCTs. The observational studies showed an increased risk of serious hemorrhage in patients discharged with AP compared with RCTs. The risk–benefit ratio is uncertain in older patients and patients with more comorbidities, and it is reasonable to assess on regular basis the risk of hemorrhage and ischemic events and if any changes in medication should be made in these patients.

The incidence of ICrH was investigated in the Riksstroke population during 1998–2009, and the incidence of all serious hemorrhages in the NAILED population during 2010–2013. Since the start periods of these trials, NOACs have become the standard choice for preventing stroke in patients with AF. NOACs are associated with a decreased risk of ICrH compared with warfarin in the RCTs but there might be an increased risk of GI hemorrhage. Observational studies show a safety profile in clinical setting similar to the RCTs. A short period with DAPT after a minor stroke or high-risk TIA may be beneficial according to two recent RCTs and will possibly be prescribed to more patients. Whether use of NOAC and DAPT will affect future rates of hemorrhage in stroke and TIA patients needs to be analysed in unselected stroke and TIA populations. Rates in different categories of patients with different age and functional levels also need to be considered. With more than 40% of patients being over age 80 years, trials that focus on this patient group are warranted.

In the NAILED trial, we showed that a simple but systematic follow-up can improve modifiable risk factors. It was designed to be implemented in clinical practice and to include a large proportion of the target population. The results should therefore be generalizable, at least in Sweden and other high-income countries. The present results from the NAILED trial show that an intervention of short duration is not enough in a target population that suffers from a long-term increased risk of new events. The effect of our intervention increased
over time. Very few participants were below targeting all measurements, including patients below target at baseline. A lifelong follow-up, similar to the practice in people with diabetes, regardless of initial risk factor levels, seems necessary to reach an acceptable quality of secondary prevention after stroke and TIA.

With increasing numbers of stroke patients in low-and middle-income countries, strategies are needed to improve secondary treatment. The NAILED strategy may be possible, but any approach must be adapted to available resources.

Long-term persistence to medication as well as any effect of the intervention on clinical events will be evaluated in coming studies within the NAILED project.
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40. Touzé E, Varenne O, Chatellier G, Peyrard S, Rothwell PM, Mas JL. Risk of myocardial infarction and vascular death after transient ischemic


regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet.* 2001;358:1033-1041


92. Glader EL, Sjolander M, Eriksson M, Lundberg M. Persistent use of secondary preventive drugs declines rapidly during the first 2 years after stroke. *Stroke*. 2010;41:397-401


98. Adie K, James MA. Does telephone follow-up improve blood pressure after minor stroke or tia? *Age and ageing*. 2010;39:598-603


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resumption in patients with anticoagulation-related intracerebral hemorrhage. *Jama.* 2015;313:824-836


156. Flynn RW, MacDonald TM, Murray GD, MacWalter RS, Doney AS. Prescribing antiplatelet medicine and subsequent events after intracerebral hemorrhage. *Stroke.* 2010;41:2606-2611


165. Okonofua EC, Simpson KN, Jesri A, Rehman SU, Durkalski VL, Egan BM. Therapeutic inertia is an impediment to achieving the healthy people 2010 blood pressure control goals. *Hypertension (Dallas, Tex. : 1979).* 2006;47:345-351


Herttau K, Martikainen P, Batty GD, Kivimaki M. Poor adherence to statin and antihypertensive therapies as risk factors for fatal stroke. *Journal of the American College of Cardiology*. 2016;67:1507-1515


Howard SC, Rothwell PM. Reproducibility of measures of visit-to-visit variability in blood pressure after transient ischaemic attack or minor stroke. *Cerebrovascular diseases (Basel, Switzerland)*. 2009;28:331-340

