Recurrent events and secondary prevention after acute cerebrovascular disease

Anna-Lotta Irewall

Department of Public Health and Clinical Medicine
Umeå University
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Original Articles

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

I: Bergström L, Irewall AL, Söderström L, Ögren J, Laurell K, Mooe T. One-year incidence, time trends, and predictors of recurrent ischemic stroke in Sweden from 1998-2010: An observational study. Submitted.

II: Irewall AL, Bergström L, Ögren J, Laurell K, Söderström L, Mooe T. Implementation of telephone-based secondary preventive intervention after stroke and transient ischemic attack - participation rate, reasons for nonparticipation and one-year mortality. *Cerebrovasc Dis Extra*. 2014;4(1):28-39.

III: Irewall AL, Ögren J, Bergström L, Laurell K, Söderström L, Mooe T. Nurse-led, telephone-based, secondary preventive follow-up after stroke or transient ischemic attack improves blood pressure and LDL cholesterol: Results from the first 12 months of the randomized, controlled NAILED stroke risk factor trial. *PLoS One*. 2015;10(10):e0139997.

IV: Irewall AL, Ögren J, Bergström L, Laurell K, Söderström L, Mooe T. Nurse-led, telephone-based secondary preventive follow-up benefits stroke/TIA patients with low education: A prospective cohort study. Submitted.

Abstract

Background Patients who experience a stroke or transient ischemic attack (TIA) are at high risk of recurrent stroke, but little is known about temporal trends in unselected populations. Reports of low adherence to recommended treatments indicate a need for enhanced secondary preventive follow-up to achieve the full potential of evidence-based treatments. In addition, socioeconomic factors have been associated with poor health outcomes in a variety of contexts. Therefore, it is important to assess the implementation and results of secondary prevention in different socioeconomic groups.

Aims The aims of this thesis were to assess temporal trends in ischemic stroke recurrence and evaluate the implementation and results of a nurse-led, telephone-based follow-up program to improve blood pressure (BP) and low-density lipoprotein cholesterol (LDL-C) levels after stroke/TIA.

Methods In study I, we collected baseline data for unique patients with an ischemic stroke event between 1998 and 2009 (n=196 765) from the Swedish Stroke Register (Riksstroke). Recurrent ischemic stroke events within 1 year were collected from the Swedish National Inpatient Register (IPR) and the cumulative incidence was compared between four time periods using the Kaplan-Meier survival analysis and the logrank test. Implementation (study II) and 1-year results (study III-IV) for the secondary preventive follow-up were studied in the NAILED (Nurse-based Age-independent Intervention to Limit Evolution of Disease) study. Between 1 Jan 2010 and 31 Dec 2013, the baseline characteristics of consecutive patients admitted to Östersund Hospital for acute stroke or TIA were collected prospectively (n=1776). Consenting patients in a condition permitting telephone-based follow-up were randomized to nurse-led, telephone-based follow-up or follow-up according to usual care. Follow-up was cunducted at 1 and 12 months after discharge and the intervention included BP and LDL-C measurements, titration of medication, and lifestyle counseling. In study II, we analyzed factors associated with non-participation in the randomized phase of the NAILED study, including association with education level. In addition, we compared the 1-year prognosis in terms of cumulative survival between participants and non-participants. In study III, we compared differences in BP and LDL-C levels between the intervention and control groups during the first year of follow-up and, in study IV, in relation to level of education (low, ≤10 years; high, >10 years).

Results The cumulative 1-year incidence of recurrent ischemic stroke decreased from 15.0% to 12.0%. Among surviving stroke and TIA patients,

53.1% were included for randomization, 35.7% were excluded mainly due to physical or cognitive disability, and 11.2% declined participation in the randomized phase. A low level of education was independently associated with exclusion, as well as the patient's decision to abstain from randomization. Excluded patients had a more than 12-times higher risk of death within 1 year than patients who were randomized. After 1 year of follow-up, the mean systolic BP, diastolic BP, and LDL-C levels were 3.3 mmHg (95% CI 0.3 to 6.3), 2.3 mmHg (95% CI 0.5 to 4.2), and 0.3 mmol/L (95% CI 0.1 to 0.4) lower in the intervention group than among controls. Among participants with values above the treatment goal at baseline, the differences in systolic BP and LDL-C levels were more pronounced (8.0 mmHg, 95% CI 4.0 to 12.1; 0.6 mmol/L, 95% CI 0.4 to 0.9). In the intervention group, participants with a low level of education achieved similar or larger improvements in BP and LDL-C than participants with a high level of education. In the control group, BP remained unaltered and the LDL-C levels increased among participants with a low level of education.

Conclusion The 1-year risk of ischemic stroke recurrence decreased in Sweden between 1998 and 2010. Nurse-led, telephone-based secondary preventive follow-up is feasible in just over half of the survivors of acute stroke and TIA and achieve better than usual care in terms of BP and LDL-C levels, and equality in BP improvements across groups defined by education level. However, a large proportion of stroke survivors are in a general condition precluding this form of follow-up, and their prognosis in terms of 1-year survival is poor. Patients with a low education level are over-represented within this group and among patients declining randomization for secondary preventive follow-up.

Enkel Sammanfattning

I Sverige inträffar årligen drygt 25 000 fall av stroke. Stroke är ett sjukdomstillstånd som innebär akut uppkommen hjärnskada till följd av minskat blodflöde till en del av hjärnan eller till följd av att ett blodkärl i hjärnan brustit och orsakat en blödning. Det nedsatta blodflödet beror vanligen på att ett blodkärl täppts till och resultatet blir akut syrebrist i den del av hjärnan som blodkärlet försörjer. Denna typ av stroke kallas ischemisk stroke och är betydligt vanligare än stroke pga blödning. I vissa fall återställs blodflödet så snabbt att skador på hjärnan aldrig hinner uppstå. Sådana episoder räknas inte som ischemisk stroke utan kallas istället för transitorisk ischemisk attack, TIA. De allra flesta som drabbas av en ischemisk stroke överlever idag, men många får bestående men och tyvärr är risken hög att drabbas av ytterligare en stroke. Det senare gäller även efter TIA och allra störst är risken under det första året. Det är därför viktigt att tidigt komma igång med förebyggande åtgärder. Läkemedel är en viktig del i den förebyggande behandlingen och innefattar långtidsbehandling med preparat för att sänka blodtryck och blodfetter samt preparat för att motverka bildandet av blodproppar. För blodtryck och blodfetter finns målnivåer mot vilka man strävar med behandlingen. För blodtryck är målnivån <140/90 mmHg. När det gäller blodfetter ändrades nyligen målnivån för det så kallade LDL (low-density lipoprotein) kolesterolet från tidigare <2.5 mmol/L till nuvarande <1.8 mmol/L. Idag har de allra flesta patienter med ischemisk stroke som skrivs ut från sjukhus förebyggande behandling men det är inte fullt klarlagt om risken att återinsjukna har förändrats över tid. Tidigare studier har dessutom indikerat att andelen patienter som når upp till de rekommenderade målnivåerna är otillfredsställande låg.

I Sverige finns ett nationellt register i vilket patienter med stroke som vårdats på sjukhus registreras. Syftet med registret är i första hand att kunna bedriva kvalitetsuppföljning och utvärdering för att förbättra vården för patienter med stroke, men registret används också till forskning. Sverige har även administrativa register över alla vårdtillfällen på sjukhus samt över dödsfall och dödsorsaker. Genom dessa register studerade vi hur risken att återinsjukna i ischemisk stroke har förändrats över tid samt vilka faktorer som verkar vara kopplade till en ökad respektive minskad risk. Våra resultat visade att risken att drabbas av en ny stroke inom ett år har minskat under den studerade tidsperioden 1998-2010. För den senare delen av perioden hade vi tillgång till uppgifter om läkemedelsbehandling vid utskrivning och vi kunde där se att användningen av läkemedel successivt ökat samt att behandling med blodfettssänkare och läkemedel för att förhindra blodproppsbildning var associerade med en lägre risk att återinsjukna. Hög

ålder, tidigare hjärtinfarkt, tidigare stroke, förmaksflimmer utan behandling för att förebygga blodproppar, diabetes samt behandling med vissa typer av blodtryckssänkande läkemedel var faktorer som var förenade med en högre risk att återinsjukna. Hur det kommer sig att blodtryckssänkande läkemedel, som ju är tänkt att vara en förebyggande behandling, var associerat med en högre risk kan vi inte säkert säga. Ett orsakssamband är dock osannolikt och istället skulle det kunna vara så att dessa läkemedel utgör en markör för högt blodtryck eller underliggande hjärtsjukdom, vilka är tillstånd där vi vet att risken för stroke är förhöjd och där behandling inte helt klarar av att normalisera denna riskökning.

År 2010 inledde vi i Jämtlands län en forskningsstudie med syfte att se om det går att ytterligare minska risken för återinsjuknande i stroke och hjärtkärlsjukdom bland patienter som just haft en stroke eller en TIA. I studien ville vi se om det genom systematisk, sjuksköterskeledd uppföljning via telefon går att förbättra nivåer av blodtryck och blodfetter ytterligare jämfört med vad som redan åstadkoms genom nuvarande uppföljning som i huvudsak bedrivs av primärvården. Vi ville även se hur stor andel av alla patienter med stroke och TIA som kunde och ville delta i den telefonbaserade uppföljningen och om resultatet av denna uppföljning respektive ”vanlig uppföljning” skiljde sig åt i grupper med olika utbildningsnivå. Studien visade att drygt en tredjedel av patienterna inte kunde delta i uppföljningen, oftast pga betydande men efter sin stroke, annan allvarlig sjukdom med kort förväntad överlevnad eller demenssjukdom. Av de som bedömdes kunna delat, tackade drygt fyra av fem ja till deltagande och dessa lottades till antingen sjuksköterskeledd, telefonbaserad uppföljning eller ”vanlig” uppföljning. Den första telefonuppföljningen skedde ca 1 mån efter utskrivning från sjukhus och innefattade genomgång av läkemedelsbehandling samt återkoppling rörande nivåer av blodtryck och blodfetter som uppmätts strax innan uppföljningstillfället. Vid behov justerades läkemedelsbehandlingen i samråd med en läkare. Vid uppföljningen diskuterades även livsstilsfaktorer såsom rökning, fysisk aktivitet och matvanor. För patienter där målnivåerna för blodtryck eller LDL-kolesterol ej var uppnådda vid 1 mån gjordes en ny kontroll och eventuellt ytterligare läkemedelsjusteringar med intervall om 4 v tills målet uppnåtts eller ingen ytterligare åtgärd var möjlig. Vid uppföljning av alla deltagarna vid 12 mån efter utskrivning kunde vi se att det genomsnittliga blodtrycket och LDL-kolesterolet i telefonuppföljningsgruppen minskat sedan kontrollen vid 1 mån. I gruppen som följts på ”vanligt” vis var det genomsnittliga blodtrycket däremot oförändrat och LDL-kolesterolet hade ökat. Vid 12 mån var både det genomsnittliga blodtrycket och det genomsnittliga LDL-kolesterolet lägre i telefonuppföljningsgruppen jämfört med i den andra gruppen. Bland

patienter som inte uppfyllde målvärdet för blodtryck vid 1 mån var skillnaden i blodtryck mellan grupperna i en storleksordning som är jämförbar med resultat i tidigare blodtrycksstudier och som visat sig kunna minska den relativa risken för stroke med ungefär en femtedel.

När vi jämförde resultaten i respektive uppföljningsgrupp mellan grupper med låg respektive hög utbildningsnivå såg vi att resultaten avseende blodtryck var likvärdiga oavsett utbildningsnivå i telefonuppföljningsgruppen medan den lågutbildade gruppen uppnådde sämre resultat än den högutbildade bland de som följts på ”vanligt” vis. När det gällde LDL-kolesterol uppnådde den lågutbildade gruppen bättre resultat än den högutbildade bland dem som följts av sjuksköterska via telefon, medan en motsatt trend sågs i den ”vanliga” gruppen.

Sammanfattningsvis visar våra resultat att risken att återinsjukna i ischemisk stroke har minskat i Sverige. Bland åtminstone hälften av alla patienter som kommer till sjukhus pga av stroke eller TIA är förbättring avseende den förebyggande behandling möjlig att åstadkomma genom sjuksköterskeledd, telefonbaserad uppföljning och detta skulle kunna leda till ytterligare riskreduktion i denna grupp. Sjuksköterskeledd, telefonbaserad uppföljning tycks också vara fördelaktig bland lågutbildade individer. Det senare är ett viktigt fynd eftersom att tidigare studier har visat att detta är en grupp med högre risk att återinsjukna i stroke. Olikheter avseende blodtrycksnivåer skulle kunna vara en bidragande orsak till att lågutbildade har högre risk att drabbas av en ny stroke, men detta, liksom andra bakomliggande mekanismer, behöver studeras närmare. Det är även viktigt att i framtiden studera om förändring avseende risken att återinsjuknande skiljer sig mellan olika typer av ischemisk stroke, om den telefonbaserade uppföljningen är framgångsrik också under längre tids uppföljning och om den, i slutänden, leder till att färre drabbas av nya fall av hjärtkärlsjukdom – vilket ju är själva syftet med den förebyggande behandlingen.

Abbreviations and Acronyms

ACE	Angiotensin converting enzyme
AF	Atrial fibrillation
ARB	Angiotensin receptor blocker
ASA	Acetylsalisylic acid
BMI	Body mass index
BP	Blood pressure
CDR	Cause of Death Register
CE	Cardioembolic
CHF	Congestive heart failure
CI	Confidence interval
DBP	Diastolic blood pressure
GFR	Glomerular filtration rate
GP	General Parctitioner
HPS	Heart Protection Study
HR	Hazard ratio
ICD	International Classification of Disease
ICH	Intracerebral hemorrhage
IHD	Ischemic heart disease
IPR	In-patient register
LAA	Large artery atherosclerosis
LDL-C	Low-density lipoprotein cholesterol
NAILED	Nurse-based Age-independent Intervention to Limit Evolution of Disease
OR	Odds ratio
PAD	Peripheral artery disease
PATS	Post-stroke Antihypertensive Treatment Study
PCSK9	Proprotein convertase subtilisin/kexin type 9
PRoFESS	Prevention Regimen for Effectively Avoiding Second Strokes
PROGRESS	Preventing Strokes by Lowering Blood Pressure in Patients With Cerebral Ischemia
RCT	Randomized controlled trial
RRR	Relative risk reduction
SAH	Subarachnoid hemorrhage
SAO	Small artery occlusion

SBP	Systolic blood pressure
SEK	Swedish krona [currency]
SEP	Socioeconomic position
SEPHIA	SEcondary Prevention after Heart Intensive care Admission
SPARCL	Stroke Prevention by Aggressive Reduction in Cholesterol Levels
SPS3	Secondary Prevention of Small Subcortical Strokes
TIA	Transient ischemic attack
VIP	Västerbotten Intervention Program
WHO	World Health Organization

Background

Definition of stroke and transient ischemic attack

Stroke is a neurological condition caused by cerebral ischemia or bleeding with permanent damage to cerebral tissue leading to sudden onset of focal or global neurological symptoms, and sometimes death. If the cerebral ischemia is transient and without apparent permanent disability, the event is considered a transient ischemic attack (TIA). According to the traditional definition of stroke from the World Health Organization (WHO) cerebral damage was considered permanent if symptoms lasted >24 h.[1] In most transient events, symptoms resolve much faster and modern neuroimaging has confirmed that approximately one-third of patients who experience a TIA based on the WHO definition have radiological signs of brain infarction, leading to the proposition of a new, tissue-based definition of stroke[2] and TIA.[3] According to the new definitions, an ischemic event with radiological or pathological evidence of acute brain infarction is classified as an ischemic stroke, whereas a TIA is an event with transient symptoms and no evidence of acute infarction. The traditional, clinical definitions of stroke and TIA are, however, still predominate in published clinical research.

Etiology and pathophysiology

The etiological and pathophysiological mechanisms resulting in stroke or TIA are heterogeneous. Ischemic stroke or TIA is generally caused by localized occlusion of an artery, which results in the obstruction of blood flow to the corresponding area of the brain and, in the case of stroke, eventually brain infarction.[4] Hemorrhagic stroke includes intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). ICH is typically caused by non-traumatic rupture of one of the small arteries penetrating the cerebral parenchyma but may also be caused by rupture of an intracranial vascular malformation or occur as a complication of other conditions, such as cerebral venous thrombosis.[5] A vast majority of SAHs are caused by rupture of an intracranial aneurysm resulting in a mass effect due to rapid expansion of the hemorrhage in the subarachnoid space and, in many cases, a disturbance in the circulation of cerebrospinal fluid.[6] SAH will not be discussed further in this thesis.

Ischemic stroke and TIA

Arterial occlusion is most commonly caused by embolism, localized thrombosis, or small vessel disease. Emboli can be of cardiac or arterial

origin and may obstruct any downstream cerebral artery, though the larger arteries are the most common sites of occlusion. Cardiac embolism typically occurs as a result of atrial fibrillation with thrombotic formation in the left atrium. Artery-to-artery emboli typically originate from intracranial and extracranial atherosclerotic plaques and cause obstruction in downstream arteries. Sudden arterial occlusion may also occur at the site of the atherosclerotic plaque itself through superimposed formation of a thrombus occluding the main vessel or through the occlusion of adjacent penetrating artery branches. The latter may occur as a result of thrombus formation, microdissection, or plaque hemorrhage. Sudden hypoperfusion, for example distal to a stenotic artery, can also occur in states of hemodynamic fluctuation and, in the absence of a compensating system of collateral arterial vessels, result in focal neurological symptoms and, in rare cases, permanent damage to the brain tissue.[4]

Infarctions due to obstructions of the small penetrating arteries are often associated with small vessel disease, a degenerative condition of the vessel wall causing luminal narrowing and reduced vessel distensibility. Associated histological findings include the degeneration of smooth muscle cells, hemorrhagic extravasation, and deposition of fibrinoid material, collagen, or other foreign material in the vessel wall.[7, 8]

Ischemic stroke may also occur as a result of artery dissection or as a manifestation of conditions such as inflammatory arteriopathies or genetic, metabolic, prothrombotic, and vasospastic disorders. These rare causes of stroke include approximately 200 different conditions and account for less than 5% of stroke cases.[9] This proportion is, however, higher among younger patients.[10-12]

Intracerebral hemorrhage

The rupture of small penetrating arteries causes bleeding into the parenchymal tissue and hematoma formation. Expansion of the hematoma within the static cranium causes the initial brain damage, followed by additional damage due to brain edema and the inflammatory and toxic responses to products of the hematoma. Most ICHs occurs in either the cerebral hemispheres (“lobar ICH”) or the deep grey matter (“deep ICH”).[5] Deep ICH is often associated with similar small vessel pathology as found in ischemic events in this region of the brain, whereas a different form of small vessel pathology called cerebral amyloid angiopathy appears to be relatively common in lobar ICH. This condition is characterized by progressive deposition of beta amyloid in the vessel wall[8] and occurs most frequently among the elderly. As mentioned above, ICH may also be caused by bleeding

from vascular malformations or be the consequence of other conditions, including cerebral venous thrombosis, brain tumors, vasculitis, and hemostatic disorders.[5]

Epidemiology

Incidence

According to data from the Framingham cohort, the lifetime risk of suffering a stroke is roughly 1 out of 5 for middle-aged women and 1 out of 6 for middle-aged men. The difference between the sexes is largely explained by a longer life expectancy among women.[13] However, stroke incidence and the proportional distribution of ischemic stroke and ICH do vary between different regions of the world,[14] and the proportional distribution of the main etiological subtypes of ischemic stroke (large artery atherosclerosis, LAA; small artery occlusion, SAO; cardioembolism, CE; and other causes) vary between ethnic groups.[15, 16] Overall stroke incidence[17-21] and the incidence of etiological subtypes is also age-dependent.[11, 12, 22-24]

In Sweden, an age-standardized incidence rate of first-ever stroke around 250-300 per 100 000 person-years at risk has been reported by different population-based cohort studies.[17, 18, 25] The incidence increases steeply with age, ranging from roughly 25/100 000 at 35-44 years of age to 2500/100 000 at ≥85 years of age.[17, 18] More than 80% of all stroke events occur among those aged 65 years or older.[26] Cerebral infarction and ICH account for approximately 88% and 12%, respectively, of the events registered in the Swedish Stroke Register, Riksstroke.[27] In a hospital-based cohort from Lund, CE, SAO, LAA, and other causes accounted for approximately 30%, 20%, 10%, and 3% of cerebral infarctions, whereas a reliable cause could not be determined for the remaining portion. Stroke due to cardiac embolization was increasingly common with age, whereas the etiological spectrum in younger age groups was more diverse with higher proportions classified as "other causes".[12]

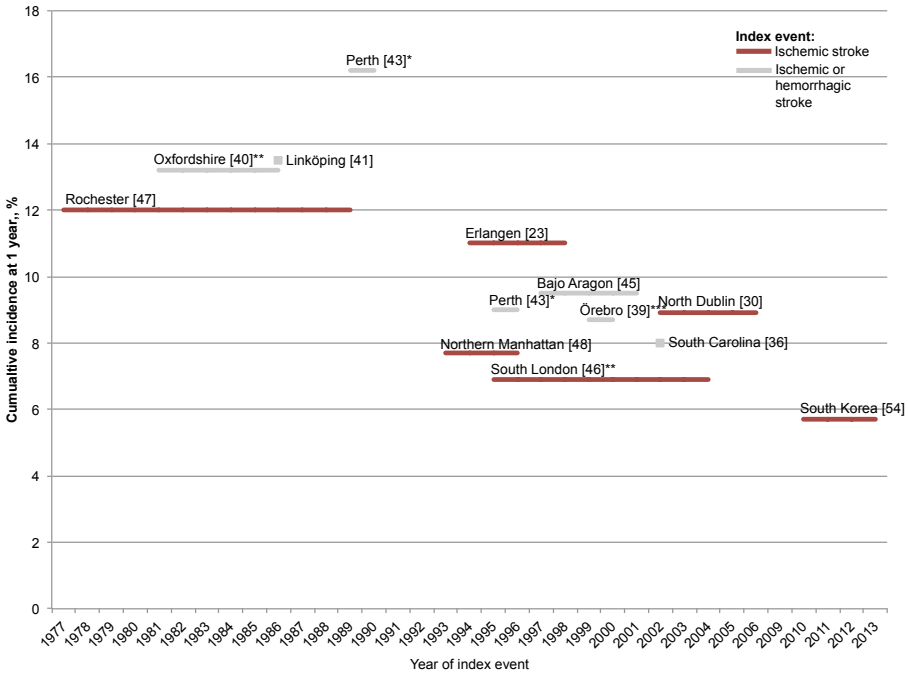
In general, high-income countries had a decreasing trend in stroke incidence between 1990 and 2010, whereas a tendency towards the opposite was observed in low- and middle-income countries.[28] In Sweden, national registry data indicate a decline in the incidence of first-ever ischemic stroke from the mid-1990s until 2010 in the 45-84 years age group, whereas an opposite temporal trend was observed among those aged 18-44 years.[29]

Prognosis

Stroke is a severe event with a high risk of persistent disability and fatality. Population-based and hospital-based studies have reported 1-month case-fatality proportions of approximately 15%[26, 30] for cerebral infarction and 30%[26, 31] or higher[30] for ICH. Among patents registered in Riksstroke (years 2001-2005) the corresponding proportions for 1-year fatality were approximately 23% and 37%.[26] Three months after a first-ever ischemic stroke, ICH, or SAH, roughly 40% of patients are dead, severely disabled, or institutionalized according to population-based data from selected regions of six European countries.[32] Similar results have been reported from Riksstroke.[33] For subtypes of ischemic stroke, prognosis in terms of 3-month disability[11, 34] and 1-month,[22] 3-month,[11] and 12-month[22] survival is best for SAO and worst for CE. Overall, long-term survival after stroke seems to have improved over time in Sweden, at least up until the beginning of the 21st century.[18, 25]

Stroke survivors and patients who have had a TIA are at high risk of subsequent cardiovascular events.[23, 30, 34-53] In Sweden, 1 in 4 strokes are recurrent events.[27] The risk of recurrent stroke is particularly high during the first year.[30, 36, 38, 40, 43, 46-48] The cumulative 1-year incidence given survival has ranged from 6% to 16% in different population-based and hospital-based cohorts (figure 1),[23, 30, 35, 36, 39-41, 43, 45-48, 54] which is several times higher than the stroke risk in the general population. Different studies have reported similar[38-40, 45, 46] or lower[30, 36, 41] occurrence of recurrent stroke in patients with ICH compared to patients with ischemic stroke. Among patients with ischemic stroke, the early risk of recurrence is particularly high after stroke due to LAA,[34, 55] though some studies have found similar recurrence estimates for patients with CE stroke.[45, 54, 56] Differences between subtypes regarding long-term risk are more uncertain,[23, 34] but patients with ischemic stroke due to small vessel disease seem to have the lowest risk.[54, 56] After an ischemic stroke, most recurrent stroke events are ischemic[30, 38, 44] but often not confined to the same etiological subtype as the primary event.[34, 44] After ICH, ischemic stroke accounts for at least half of recurrent stroke events.[31, 38, 42]

Figure 1 Cumulative 1-year incidence of recurrent stroke in population-based and hospital-based cohort studies



All studies calculated cumulative incidence using life table analysis or Kaplan-Meier analysis with censoring for death. Recurrent events included ischemic stroke, intracerebral hemorrhage and, sometimes, subarachnoid hemorrhage. *Did not count events that occurred during the first 21 days. **Did not count events that occurred during the first 21 days unless it could be established that the event corresponded to a different vascular territory than the index event. ***Did not count events that occurred during the first 28 days.

A comparison of individual studies gives the impression of a gradual decrease in the 1-year cumulative incidence of stroke recurrence over time (figure 1). However, an analysis and comparison of recurrence risk is complex, as differences in population characteristics and temporal trends in diagnostics, hospitalization, and mortality rates have to be taken into account. In addition, differences in the definition of index and recurrent events make comparisons difficult. Some studies have assessed temporal trends in stroke recurrence and point to a decrease in some regions and countries.[38, 43, 49-52, 57, 58] For example, the 1-year incidence rate of ischemic stroke recurrence decreased by 30% (relative risk reduction, RRR) in the Italian region of Lombardy between the years 2002 and 2010.[52] Similarly, an 18% decrease in the cumulative incidence was observed in Taiwan from 2000 to 2011.[50] Most of the other available time trend studies have included both ischemic and hemorrhagic index events,[38, 43, 51, 57] some of the cohorts were small[43, 47] and some were age-restricted.[38, 49, 58] In Sweden, recent

studies have reported a decrease in early and long-term ischemic[58] and ischemic/hemorrhagic[38] stroke recurrence in later years for the 18-54 years[58] and 25-74 years age groups,[38] but whether this trend extends to a population without an upper age limit is currently not known.

Risk factors

Several factors are associated with the risk of stroke, and many are potentially modifiable. Among the modifiable risk factors, blood pressure (BP) is regarded as the most important. Other factors include current smoking, waist-to-hip ratio, diet, physical inactivity, diabetes mellitus, alcohol consumption, psychosocial factors, dyslipidemia, and atrial fibrillation.[59] The relative importance of individual risk factors varies between stroke subtypes,[11, 22, 23, 26] and there is a disproportionate distribution of stroke risk between various socioeconomic groups.[60-64]

Blood pressure

Data from the first Framingham cohort were published in 1970, showing that BP levels among men and women aged 30-59 years were associated with stroke incidence during a subsequent 14-year follow-up. In this population, the risk of stroke associated with BP was sex- and age-independent and increased proportionally with increasing baseline BP.[65] Numerous cohort studies in different settings have been published thereafter, and meta-analysis has shown a continuous positive association between BP and stroke mortality down to at least 115/75 mmHg. Based on the same meta-analysis, a 20 mmHg difference in systolic BP (SBP) is associated with a 50% relative difference in the risk of stroke at 70-79 years of age.[66] The association with hypertension seems to be strongest for ICH[59] and ischemic stroke due to SAO.[11, 23] Swedish population-based cohort studies have shown that hypertension in middle-age is a risk factor for stroke during 18[ref. 67] and 28[ref. 68] years of follow-up, and that BP >140/90 is an important risk factor for stroke also among those >85 years of age.[69] In a meta-analysis of randomized controlled trials (RCTs), a SBP reduction of 10 mmHg through antihypertensive treatment was associated with a 31% RRR of stroke over a mean follow-up of 4.5 years.[70]

In addition to high BP, visit-to-visit BP variability has been identified as an independent risk factor for stroke.[71] Variability in BP seems to be particularly high among patients with a previous stroke,[72] and one study reported that up to 58% of stroke patients with a single normal SBP measurement at an office visit had a mean SBP above the treatment target in repeated measurements over 1 year.[73]

Serum cholesterol

The main components of total serum cholesterol are low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, and triglycerides.[74] In meta-analyses of prospective observational studies, cholesterol levels were positively associated with fatal and non-fatal ischemic stroke, whereas hemorrhagic stroke seemed to have an inverse association.[75, 76] A 1 mmol/L difference in LDL-C was associated with a 15% relative difference in ischemic stroke incidence.[75] Another meta-analysis found a weak positive association only for those <70 years of age, but this study only analyzed fatal stroke events and had several weaknesses. One such weakness was that, in a majority of cases, only measures of total cholesterol were available. In addition, the analyses by stroke subtype had limitations because no information on subtypes was reported for nearly half the population, confirmatory diagnostics for ischemic and hemorrhagic events were seldom available, and ischemic stroke subtypes were not analyzed separately.[76] The latter is problematic, as the etiology of stroke is heterogeneous[4, 5] and the distribution of ischemic stroke subtypes strongly age-dependent.[11, 12, 22-24] Furthermore, case-fatality rates differ substantially by stroke subtype, which makes it difficult to evaluate the association between stroke and cholesterol levels based only on fatal events. Few studies have analyzed cholesterol levels by ischemic stroke subtype, but a positive association between high cholesterol and carotid stenosis[77] and LAA stroke has been reported.[78]

In meta-analyses of RCTs, a 1 mmol/L reduction in LDL-C reduced the relative risk of stroke by approximately 20%, but with no preventive effect on hemorrhagic stroke events.[74, 75]

Socioeconomic position

Socioeconomic position (SEP), which refers to social and economic factors that influence what position individuals and groups hold within the structure of society,[79] is an important risk marker for cardiovascular disease.[60-64, 80-82] Indicators commonly used to measure SEP include education level, income, occupational class, and housing conditions.[83, 84] Low SEP has repeatedly been associated with a higher prevalence of cardiovascular risk factors[63, 80, 85, 86] and subclinical atherosclerosis,[80, 85] as well as a higher incidence of stroke[60-64] and other cardiovascular events.[64, 80, 81] In Sweden, low SEP has been associated with an elevated risk of both first-ever stroke[61, 63, 64] and stroke recurrence.[87, 88] Among individuals <70 years of age, occupational differences in the incidence rate of first time ischemic stroke were stable or increased between 1997 or 2002 and 2010.[64] Similarly, the differences in cumulative risk of stroke recurrence was sustained between groups defined

by education and income levels during the same approximate time period.[87] The association between SEP and cardiovascular disease is not completely understood, but generally thought to be mediated through differences in health behavior and lifestyle, environment, and access to and/or utilization of health care resources.[89] Among stroke patients, those with low SEP have a higher prevalence of cardiovascular risk factors according to several studies.[60, 62, 82, 90] However, whether the control of modifiable risk factors differs between socioeconomic groups during long-term follow-up is unknown.

Secondary preventive treatment

The absolute annual number of stroke events has been predicted to increase over the next few decades due to a continuous increase in total life expectancy[17, 18] and population growth.[18] If survival after stroke continues to improve,[18, 25] it will further contribute to increasing stroke prevalence in the Swedish population and an increased need for secondary preventive treatment. For long-term secondary prevention, current guidelines include recommendations regarding antihypertensive and lipid-lowering treatment, as well as treatment with antiplatelet agents and oral anticoagulants. Advice regarding lifestyle adjustments, such as increased physical activity, smoking cessation, and improved nutrition, is also given.[91, 92]

Antihypertensive treatment

Antihypertensive treatment is recommended after ischemic stroke, TIA, and ICH. Current recommendations build on evidence from numerous prospective cohort studies[66] and placebo-controlled randomized trials[93] from the 1960s onwards. Meta-analysis of RCTs suggests that a BP difference of 5.1/2.5 mmHg is associated with a 22% reduction of risk for recurrent stroke favoring active treatment.[93] Included among these trials was PROGRESS, which compared active treatment with perindopril alone or in combination with indapamide to placebo. The results published in 2001 showed that treatment with perindopril and indapamide resulted in a BP difference of 12.3/5.0 mmHg between groups and a RRR of 43% and 40% for recurrent stroke or major vascular events, respectively.[94] In the preceding PATS trial, treatment with indapamide alone compared to placebo resulted in a BP difference of 6.8/3.3 mmHg and a 30% RRR for stroke.[93] Differences in BP between treatment arms in later trials have generally been more modest[93, 95-99] and the risk reduction smaller and non-significant.[96, 97] This is likely due, at least in part, to an increased use of open-label antihypertensive treatment across treatment arms.

Unfortunately, little evidence is available to guide treatment recommendations regarding optimal BP levels in secondary prevention after stroke. Because few studies have randomly assigned participants to treatments aiming at different target BP levels, current guidelines rely mostly on observational data and post-hoc analysis of RCTs. As previously mentioned, observational data from prospective cohort studies have suggested a benefit of BP reduction regardless of baseline BP down to at least 115/75.[66] Post-hoc analyses of the PROGRESS[100] and PRoFESS[101] trials indicated the same. In the PROGRESS trial, a significant benefit of active combination therapy was observed regardless of baseline BP down to 120 mmHg. The higher the baseline SBP, the larger the BP reduction achieved with treatment, and the lower the BP achieved, the lower the annual stroke rate.[100] In the PRoFESS trial, a BP of 140-149 mmHg was associated with a 24% higher relative risk of major cardiovascular events compared to a BP of 130-139 mmHg in patients with a recent non-cardioembolic ischemic stroke.[101] Only one RCT that randomly allocated stroke patients to different BP treatment targets has been published to date, the SPS3 trial. In this trial, no significant benefit of treatment aiming at BP <130 mmHg compared to 130-149 mmHg was seen among patients with lacunar cerebral infarct.[102]

For most patients who have suffered a stroke, current guidelines recommend antihypertensive treatment with a BP target of <140/90 mmHg.[91, 92, 103] Preceding guidelines from the past 20 years have recommended the same or even lower BP targets for secondary prevention. For example, the European Society of Cardiology expressed in their guidelines from 1998,[104] 2003,[105] and 2007[ref. 106] that lower BP should be aimed for or at least considered in patients with established vascular disease, and the Amarican Heart Association/American Stroke Association previously recommended antihypertensive treatment for all TIA and stroke patients, regardless of baseline BP, without a specified treatment target (guidelines issued in 2006 and 2011).[107, 108] For patients with diabetes or chronic kidney disease, a BP target of <130/80 mmHg was considered appropriate by most guidelines up until 2012.[106, 109-111] Thereafter, most guidelines changed the target to 140/85 mmHg,[92, 103, 112] or 140/80 mmHg[113] for most diabetic patients.

Lipid-lowering treatment

Treatment with statins is recommended for secondary prevention in ischemic stroke and TIA patients, but not routinely after ICH unless atherosclerotic disease is evident or another indication for treatment present.[91, 92] The SPARCL trial published in 2006 showed that treatment with atorvastatin (80 mg) reduced the relative risk of ischemic stroke and major coronary events by 22% and 35%, respectively. The SPARCL trial

included patients with a non-cardioembolic ischemic stroke or ICH within 6 months prior to randomization and is the only published statin trial designed solely for secondary prevention after stroke.[114] In the subgroup of participants with previous cerebrovascular disease in the preceding HPS trial, treatment with simvastatin reduced the incidence of major coronary events by 20% but did not significantly alter the risk of ischemic stroke. The time past between the qualifying event and inclusion in this trial was 4.3 years.[115] In the SPARCL trial, active treatment was associated with an increased risk of ICH, and a similar, but non-significant, trend was seen in HPS.[114, 115] Addition of PCSK9 inhibitors[116] or ezetimibe[117] to statin treatment further reduces LDL-C levels, but whether these or other lipid-modifying treatments[91] are beneficial in secondary prevention after stroke is currently unclear. There are also limited evidence guiding recommendations regarding the optimal treatment target for LDL-C levels, as there are no published trials comparing lipid-lowering treatments aiming for different treatment targets.

Since 2012, European guidelines have recommended a LDL-C target of <1.8 mmol/L (or a 50% reduction)[92, 112] and this level was also introduced into Swedish guidelines (Läkemedelsverket)[103] in 2014. Before then, the target LDL-C level for most high-risk patients was <2.5 mmol/L.[105, 106] American guidelines previously had a treatment target of <70 mg/dL (<1.8 mmol/L) for LDL-C.[108] In the most recent version of the guidelines (2014), intensive lipid-lowering treatment is recommended regardless of LDL-C level and with no specified treatment target.[91]

Antiplatelet therapy

Treatment with antiplatelet drugs reduce the risk of recurrent stroke by approximately 25% compared to placebo[118] and is recommended for all patients with non-cardioembolic ischemic stroke or TIA unless there is a strong contra-indication, mainly a high risk of bleeding. Treatment with acetylsalicylic acid (ASA) in combination with dipyridamole is slightly superior to treatment with ASA alone,[119] whereas the preventive effect of clopidogrel is comparable to ASA plus dipyridamol.[120] Current guidelines recommend treatment with any of these three options.[91, 92] Antiplatelet therapy has been an established treatment for secondary prevention of cardiovascular disease since the 1990s.[121, 122]

Oral anticoagulation

In patients with ischemic stroke and atrial fibrillation, treatment with warfarin reduces the relative risk of recurrent stroke by 68% compared to

placebo.[123] During the last few years, several new oral anticoagulants with comparable preventive effects and a slightly lower risk of bleeding have been introduced (e.g., dabigatran, apixaban, edoxaban, and rivaroxaban).[124] Unless there are contra-indications, oral anticoagulation is recommended for all cardioembolic stroke and TIA patients, though the priority between available agents varies slightly among different guidelines.[91, 125] In Sweden, the new oral anticoagulants were introduced in 2011[126] and have been given the same priority as warfarin since 2015.[127]

Secondary prevention in clinical practice

In Sweden, large proportions of patients with stroke or TIA are prescribed secondary preventive drugs at discharge,[128] but little is known about the extent to which patients achieve the recommended treatment targets for BP and LDL-C during long-term follow-up. In a study from Malmö, only 49% and 62% of patients with stroke had a BP<140/90 mmHg or LDL-C<3 mmol/L, respectively, 12 months after discharge from the hospital stroke unit.[129] Slightly better control of risk factors has been reported for other populations at very high risk of cardiovascular disease, including patients with diabetes[130] or previous myocardial infarction.[131] However, these population samples did not include patients aged >70 and >74 years, respectively. [130, 131]

In observational studies from countries other than Sweden, 24-49% and 14-77% of patients reached the treatment targets for BP and LDL-C 6 months to 3 years after hospital discharge.[56, 132-135] Although there are few data from unselected stroke and TIA populations, available studies from Sweden and other countries indicate room for improvement in secondary prevention through the optimization of treatment to lower BP and LDL-C levels. To what extent the control of risk factors could be improved in an unselected stroke and TIA population is unknown, as is the potential of such improvements to reduce the risk of recurrent stroke events.

Barriers to implementation of secondary preventive treatment

There are several possible reasons why patients do not reach treatment targets. The secondary preventive follow-up may lack continuity and/or fail to intensify treatment when targets are not met. Other important factors may be low health literacy and poor adherence and/or persistence to secondary preventive treatment.

Adherence is defined by the WHO as "the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes - corresponds with agreed recommendations from a health care provider."[136] If a patient stops taking a prescribed drug, this is usually referred to as non-persistence.[137] Although the true extent to which patients take their prescribed medication in accordance with instructions is difficult to assess,[138] available studies indicate that adherence and/or persistence to antihypertensive and lipid-lowering treatment is often suboptimal.[139-143] In studies measuring adherence by direct methods, non-adherence was found in 19-86.1% of subjects with an insufficient response to antihypertensives, despite concurrent treatment with multiple agents and self-reported full adherence.[138]

The WHO identifies five important aspects of adherence: patient-related factors, condition-related factors, therapy-related factors, social and economic factors, and health care team and system-related factors.[136] Unsurprisingly, the patient's perception of the necessity of treatment has been identified as an important, patient-related predictor of adherence.[144, 145] According to qualitative data, not knowing what the secondary preventive drugs are for, low expectations about the benefits of treatment, and worries about potential side effects may be important barriers to adherence among stroke and TIA patients.[144, 146] Other concerns include a fear of potential harm with long-term treatment,[147] suspicion that doctors over-prescribe medicines,[144] and a perception of having to many pills to take.[147] As for condition-related factors, long-term preventive treatment of chronic conditions that are mostly asymptomatic, such as hypertension and hyperlipidemia, are challenging because the patient's perception of the need for treatment is often influenced by the presence of symptoms.[136, 147] Although previous experience with cardiovascular events has been identified as being positively associated with the perception of necessity and adherence to treatment,[145, 148] previous stroke may also constitute a condition-related barrier due to high prevalence of post-stroke depression[149-151] and cognitive impairment affecting memory and executive functioning.[149, 150] Institutional living, having support from next-of-kin,[151] or having a scheduled follow-up visit to a neurologist or primary care physician[152] are positively associated with persistent drug use among stroke patients, whereas complexity of the treatment regime and lack of support in the everyday routine seem to negatively affect adherence.[141, 153, 154] This indicates that structured support of secondary preventive treatment is important to optimize adherence and persistence among stroke survivors.

Low health literacy[155] may constitute another barrier in the implementation of optimized secondary preventive treatment. The concept of health literacy

includes the ability to communicate and engage with health care providers and the consideration of information regarding health recommendations.[156] For example, health literacy may affect adherence to medication[157] and self-management.[158] Low health literacy has been found to be prevalent among patients with chronic disease, particularly in groups with low levels of education.[156]

Physicians not intensifying medical treatment despite repeated measurements above the treatment target seems to be a widespread phenomenon within primary health care according to several studies[134, 159, 160] and is referred to as therapeutic inertia.[161] Although the decision to abstain from intensifying treatment may sometimes be appropriate based on clinical judgment,[162] this is unlikely to be the explanation in all cases. The decision may be influenced by several factors related to the treating physician, the patient, and the system for provision of care.[163] Physician-related factors may include insufficient knowledge of or disagreement with current guidelines and uncertainty regarding whether the recommendations are applicable in clinical practice. The perception that it is unnecessary to intervene when values are close to the target also seems to be common. Lack of time during consultations and competing patient demands may also result in down-prioritization of risk factor management.[162, 164, 165] Patient-related factors may include unwillingness to intensify treatment or apparent non-adherence to existing treatment.[164] In Sweden, almost 80% of stroke survivors are followed up by a doctor within the year after discharge according to self-reported survey data from the Swedish Stroke Register.[166] However, the intensity of follow-up is unknown, as well as the extent to which therapeutic inertia may contribute to poor control of risk factors.

Interventions to improve blood pressure and LDL-C levels after stroke/TIA

Multiple attempts have been made to improve BP and LDL-C levels through interventions targeting different barriers in the implementation of secondary prevention after stroke/TIA.[129, 167-172] Considering the limited resources of public health care and the high prevalence of chronic cerebrovascular disease, greater involvement of health care professionals other than physicians in risk factor optimization may be a cost-effective alternative and even imperative for enhanced secondary preventive follow-up to be implemented in clinical practice. Cardiovascular prevention programs delivered by nurses or pharmacists have been evaluated in several RCTs.[129, 167, 172-175] Results are varied, and the important characteristics of successful interventions are not easily distinguished because interventions have been heterogeneous in design and the studies sometimes underpowered. In the

secondary preventive setting, most successful follow-up programs have involved the possibility of adjusting pharmacological treatment, either by involving a physician or by delegating the prescribing activities to the nurse/pharmacist.[168, 172, 175-177] Other elements have been risk factor assessment and education, review of treatment, lifestyle counseling, strategies to improve adherence, and follow-up of general well-being and concerns. With few exceptions,[178] follow-up of stroke or TIA patients that does not involve medication adjustments have not significantly improved BP or LDL-C levels,[129, 167, 179-185] despite recourse-intensive intervention designs in many cases.[179, 180, 182-185] Successful follow-up interventions have often involved relatively frequent follow-up visits, but whether this is an obligate feature cannot be established from the available data.

For an intervention to be cost-effective, it needs to be broadly implementable in clinical practice, or at least reach out to those that will gain the most (i.e., those at highest risk). Complex, high-intensity interventions are demanding, not only for the health care system, but also for the patient. Those at highest risk may also be those with the fewest personal resources to engage in health-promoting interventions. For example, interventional attempts to reduce social inequality in health outcomes may in fact widen the gap.[186, 187] Therefore, feasibility and results should be monitored across socioeconomic groups, and there is probably a reason to keep follow-up procedures as simple as possible to maximize participation.

Different means of remote communication may offer a way to increase the availability of health care interventions, especially in rural areas and among patients with reduced mobility. Telephone calls are perhaps the simplest form of remote communication, and it has been an integrated part of follow-up in many interventional studies to improve the control of cardiovascular risk factors, including a few with positive outcomes.[167, 175] There are also other areas within health care in which telephone-based interventions have been successful, such as in the follow-up and support of patients with congestive heart failure.[188]

Summary of Background

- ✓ Patients with a previous stroke or TIA are at high risk of recurrent stroke events, but there is limited data from recent years describing time trends and predictors of recurrence among unselected ischemic stroke patients.

- ✓ Antihypertensive and lipid-lowering treatments are effective in the prevention of stroke and other cardiovascular events, but many patients do not reach recommended treatment targets for BP and LDL-C, indicating a need for improved follow-up.

- ✓ Low socioeconomic groups have a higher risk of stroke recurrence, which could indicate inequality in secondary preventive care. However, whether the control of modifiable risk factors differs between socioeconomic groups after stroke/TIA is unknown.

- ✓ Nurse-led follow-up including life-style counseling and adjustment of pharmacological treatment may be a way to improve BP and LDL-C levels in secondary prevention after stroke/TIA, but this needs to be studied further.

- ✓ The potential of a secondary preventive intervention to reduce the total burden of recurrent cardiovascular events depends on how broadly it can be implemented in clinical practice. Therefore, it is essential to study feasibility in an unselected population and to assess results across socioeconomic groups.

Aims

The aims of this thesis were to:

1) Analyze the risk of suffering a recurrent ischemic stroke within 1 year, factors associated with recurrence, and whether the risk of ischemic stroke recurrence has changed in Sweden over time.

2) Describe the feasibility of nurse-led, telephone-based secondary preventive follow-up in an unselected stroke and TIA population by assessing baseline characteristics, participation rate, and factors associated with non-participation.

3) Investigate whether a nurse-led, telephone-based follow-up is more efficient than usual care at improving risk factor levels (BP and LDL-C) in stroke/TIA patients 1 year after hospital discharge.

4) Investigate the impact of nurse-led secondary prevention and usual care on risk factor differences (BP and LDL-C) 1 year after hospital discharge between stroke/TIA patients with different levels of education.

Materials and Methods

Study design, population, and outcome

Table 1 summarizes the study design and defines the population and outcome variables for each of the four studies.

Setting

Health care in Sweden

The Swedish health care system includes universal coverage and subvention of medication for all citizens. The system is publicly financed and provides inpatient and outpatient health care to all citizens at a low cost. Inpatient care is up to 100 SEK per day. The cost for out-patient consultations or visits to the emergency department varies between clinics and counties, but is usually ~100-300 SEK per visit up to the high-cost protection threshold, which is currently 1100 SEK per 12-month period.[189] There is also a national system for stepwise subsidizing of medical drugs.[190]

According to the national stroke guidelines, all patients with stroke and most patients with TIA should receive acute care at a hospital stroke unit.[191] There are currently 72 hospitals that treat acute stroke patients, and previous studies have reported that >90% of all patients with acute stroke are hospitalized,[192] or at least evaluated at the hospital.[193] Those not treated at the hospital include patients who die outside of the hospital, patients who do not seek acute care for stroke symptoms, and fragile elderly at nursing homes with short life expectancy.[192, 193]

Jämtland

Östersund hospital is the only hospital in the county of Jämtland (figure 2) and, thus, the only referral center in the county for patients with suspected stroke or TIA. The hospital has a stroke unit in which a majority of stroke and TIA patients are treated. Primary health care is provided by 28 primary health care centers spread over the county. When the NAILED (Nurse-based Age-independent Intervention to Limit Evolution of Disease) study began in 2010, Jämtland had 126 691 inhabitants, or 1.3% of the total Swedish population. The county is sparsely populated with 35.0% living in the centrally located city of Östersund, 23.0% in villages of 500-4000 inhabitants, and the remaining 42.0% in the more sparsely populated

surroundings. Official demographics[194] for county inhabitants compared to the total Swedish population are given in table 2. ‘

Table 1 Study design and populations for studies I-IV

Study	Design	Data source	N	Inclusion period	Inclusion criteria	Outcome
I	Hospital-based cohort study (with reference population)	Riksstroke, IPR, CDR, National Civil Register	196 765 (+ 190 157)	Jan 1 1998 to Dec 31 2009	Acute event of first-ever or recurrent IS (i.e. cerebral infarction, ICD-10 code I63, or “unspecified”, ICD-10 code I64)	1) 1-year incidence of recurrent IS, 2) difference in 1-year incidence of IS between time periods (1998-2000, 2001-2003, 2004-2006, 2007-2009), 3) factors associated with recurrent IS
II	Hospital-based cohort study	NAILED, CDR	887	Jan 1 2010 to Dec 31 2011	Acute event of stroke (IS or ICH) or TIA.	1) Participation rate, 2) reasons for non-participation, 3) factors associated with exclusion or decision not to participate, 4) difference in 1-year survival between participants and non-participants.
III	RCT	NAILED	537	Jan 1 2010 to Jun 30 2012	1) Acute event of stroke (IS or ICH) or TIA and 2) general condition permitting participation in telephone-based secondary preventive follow-up and 3) written, informed consent to participate in the randomized controlled NAILED stroke risk factor trial.	1) Mean difference in SBP, DBP, LDL-C between the IG and the CG at 12 months, 2) mean change in SBP, DBP and LDL-C from baseline until 12 months within the IG and the CG, 3) difference in proportions reaching the treatment target for each outcome variable.
IV	Hospital-based cohort study	NAILED	771	Jan 1 2010 to Dec 31 2013	1) Acute event of stroke (IS or ICH) or TIA and 2) general condition permitting participation in telephone-based secondary preventive follow-up and 3) written, informed consent to participate in the NAILED stroke risk factor trial and 4) completion of the first 12 months of follow-up.	1) Mean diff. in SBP, DBP and LDL-C) at 12 months between participants with high and low education level. 2) The mean change in SBP, DBP and LDL-C between baseline and 12 months within each education level group

IPR, The Swedish In-patient Register; CDR, The Swedish Cause of Death Register; NAILED, Nurse-based, Age-indepenedent Intervention to Limit Evolution of Disease; RCT, randomized controlled trial; TIA, transient ischemic attack; ICH, intracerebral hemorrhage; IS, ischemic stroke; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; IG, intervention group; CG, control group;

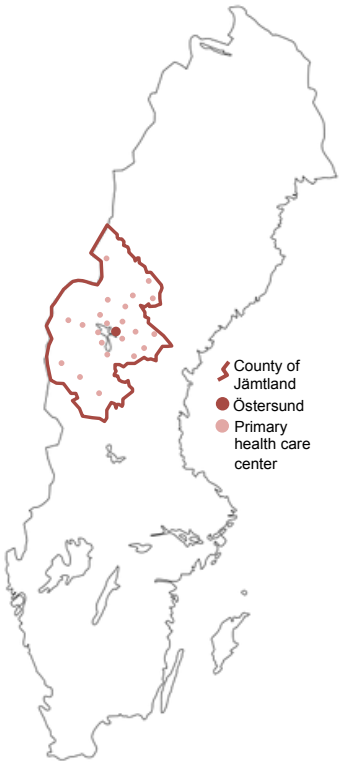


Figure 2 Map of Sweden with the borders for the county of Jämtland and the location of Östersund hospital and surrounding primary health care centers

Table 2 Demographics in 2010 in Jämtland and nationally

	County of Jämtland	**Sweden**
No. of inhabitants	126 691	9 415 570
Mean age, years	43.1	41.1
Women	50.0 (63 338)	50.2 (4 725 326)
Level of completed formal education*		
Compulsory school (≤10 years)	25.3 (26 430)	25.2 (1 909 984)
Upper secondary school or higher	74.7 (77 865)	74.8 (5 664 247)
Aged >65 years	21.2 (26 841)	18.5 (1 737 246)
Women	54.2 (14 546)	55.1 (957 468)
Level of completed formal education		
Compulsory school (≤10 years)	46.3 (12 328)	44.4 (756 723)
Upper secondary school or higher	53.7 (14 273)	55.6 (947 968)

Data are presented as % (n) unless otherwise noted. Official demographic data obtained from Statistics Sweden Oct. 31, 2016. *For inhabitants 16 years or older.

The Swedish school system

Since 1962, compulsory school in Sweden has consisted of 9-10 years of elementary school followed by 2-4 years of optional upper secondary school/vocational school leading to a vocational degree or qualifying for college and university studies. All levels of public school are free of charge. During the preceding three decades, the school system was more complex; compulsory school ranged from 6-8 years and was free of charge, but qualification for upper secondary school and university required graduation from a partly parallel school system. Altogether, 9-10 years of school was required to proceed to upper secondary school and, thereafter, university.[195]

Data sources

Riksstroke

For study I, the Swedish Stroke Register, Riksstroke, was the source of data for index ischemic stroke events, baseline characteristics, and medication at discharge. Riksstroke is 1 of currenly 96 national quality registries in Sweden with the overall aim of monitoring health care quality and stimulating improvements in care by providing feedback on measured quality indicators.[196] Riksstroke is a hospital-based registry established in 1994 and steered by a national committee of experts with Västerbotten County Council as the responsible authority. The registry is publicly funded through grants from the National Board of Health and Welfare and the Swedish Association of Local Authorities and Regions.[197] Acute ischemic (I63), hemorrhagic (I61), and unclassified (I64) stroke events qualify for registration, including variables of acute stroke care and variables from follow-up surveys performed 3 and 12 months after hospital discharge. Reporting is conducted by hospital staff (doctors/nurses/administrative staff) based on information from the patients' medical records. In addition to its primary role as a quality register, Riksstroke also provides data for research. Since 1998, all hospitals in Sweden who treat patients with acute stroke report to Riksstroke. The yearly number of reported events increased gradually during the first years, reaching a steady number of approximately 25 000 events a year since 2003.[197] Validation against the Swedish National Inpatient Register (IPR) found that the completeness of Riksstroke (the number of events registered in Riksstroke divided by the total number of events registered in Riksstroke and/or IPR) was 89.5% in 2014,[198] and the proportion of false-positive diagnoses in Riksstroke was previously estimated to be 1.4% by another validation study.[199] Validation of the accuracy in reporting acute phase variables revealed generally good inter-hospital reliability, with <5% incorrect coding for most variables.[198] The reported coverage of the registry

for 1998 to 2009 is given in table 3. Notably, the method used to calculate coverage changed in 2007. From 1998 to 2006, coverage was calculated as the number of reported stroke events divided by the expected number of events assuming that the stroke incidence was (250-)300 per 100 000 person years at risk. Using this method, the reported coverage was likely overestimated.[192, 199, 200] From 2007 onwards, coverage was calculated by relating first time events registered in Riksstroke to the corresponding number of events registered in the IPR.[201]

Table 3 Coverage of Riksstroke according to the 1998-2009 annual reports

Year	Coverage	
	Epidemiological estimate*	Comparison to NPR
1998	*Not reported*	-
1999-2000	75-80%	-
2001-2002	80%	-
2003	80%	-
2004	88%	-
2005	93%	-
2006	90%	-
2007		82%
2008		83%
2009		85%

NPR, National Patient Register. *Assuming that the stroke incidence was (250-)300 per 100 000 person years at risk.

The Swedish In-patient Register

In study I, the Swedish IPR was the source of data for recurrent ischemic stroke events and for cardiovascular events (myocardial infarction, ischemic stroke) up to 7 years prior to the index event. The IPR is part of the National Patient Register, a national administrative registry maintained by the National Board of Health and Welfare. The IPR contains hospitalization-related variables, including admission and discharge dates and discharge diagnoses. Registration has been mandatory for all Swedish hospitals since 1984, and since 1997 diagnoses has been classified according to the 10th revision of the International Classification of Disease (ICD-10).[202] The IPR has been validated by multiple studies.[203] A validation study of stroke diagnoses registered in the National Patient Register in northern Sweden during 2004 found that 88.1% of acute stroke diagnoses were correct in the sense that they referred to hospitalization for a new acute stroke event. The sensitivity was 82.7%. Among acute stroke events not registered, 46% were fatal events identified through the Cause of Death Register (CDR).[204] Another validation study found very similar validity for events registered during the first 6 months of 1998.[199] The validity (positive predictive value

74.3%) and sensitivity (74.5%) of recurrent acute stroke events seem to be less than corresponding measures for first-ever events.[204] According to the ICD-10, an acute stroke diagnosis (I61, I63, I64) may be used for hospitalizations up to 12 months after the acute event.[205] Based on one study, use of an acute stroke diagnosis when a patient with a previous stroke was re-hospitalized without the occurrence of a new stroke event seems to account for most "incorrect" acute stroke diagnoses.[199] The transfer of a stroke patient between hospitals or hospital units also generates multiple registrations referring to the same acute event. We included the first ischemic stroke event (I63, I64) occurring within 1 year after admission for the index event, but excluded events with a date of admission to a rehabilitation facility immediately adjacent to the hospitalization for the index ischemic stroke event.

The Swedish Cause of Death Register

In studies I and II, the Swedish CDR was used to obtain mortality data for the study population during follow-up. The CDR is a national administrative registry maintained by the National Board of Health and Welfare. The registry contains mortality data for Swedish residents from 1961 onwards. The registered data are based on death certificates and the cause of death coded according to the ICD.

Statistics Sweden

For study I, the administrative authority Statistics Sweden created a matched reference population in order to relate time trends in ischemic stroke recurrence to time trends in stroke incidence in the general population. To preserve the representativeness of the general population, we did not exclude reference subjects with prior stroke or other comorbidities. The reference population was created by randomly matching (1:1) each individual in the Riksstroke cohort to an individual of the same age, sex, and county of residence in the National Civil Register. The reference group was matched with the stroke cohort by January 1 of the year the stroke patient suffered the index stroke. Some subjects in the reference group died before the date of the corresponding index stroke (n=5763), and it was impossible to find a matching control in some cases (n=845). Therefore, the reference group was somewhat smaller than the stroke cohort.

The NAILED study

Studies II-IV were conducted as part of the NAILED study. Between January 1, 2010, and December 31, 2013, consecutive patients admitted to Östersund

Hospital due to acute stroke (brain infarction or ICH) or TIA were prospectively assessed for baseline characteristics and the ability to participate in telephone-based secondary preventive follow-up (figure 3). Stroke and TIA diagnoses were made by clinical physicians not involved in the study, whereas the identification and assessment of patients with a final diagnosis of stroke or TIA was performed by study nurses. The study nurses identified patients through daily reviews of hospital records for patients who underwent computed tomography brain scans and patients hospitalized at the stroke unit. The study nurses collected baseline data through patient interviews and reviews of medical records. Patients in a condition permitting telephone-based follow-up were extended an offer to participate in the randomized phase of the study in which consenting patients were allocated (1:1) to nurse-led, telephone-based follow-up (intervention) or follow-up according to standard care (control). The randomization allocation sequence was computer generated in blocks of four and stratified for sex and the degree of disability (modified Rankin Scale 0-2 or 3-5). The resulting group allocation was not blinded to participants, the study team, or other caregivers. For patients excluded from the randomized phase, the study nurses documented the main reason for exclusion among eight pre-specified alternatives (table 4).

All randomized participants were contacted 1 and 12 months after hospital discharge. Baseline (i.e., 1 month after hospital discharge) and follow-up measurements of BP and blood lipids were performed by health care professionals at the participant's closest health care facility and reported to the study team. Seated BP was measured after 5 min of rest. LDL-C was calculated from serum concentrations of cholesterol and fasting triglycerides using the Friedewald formula. Shortly thereafter, a study nurse telephoned participants in both groups and interviewed them about their sense of well-being, use of tobacco, level of physical activity, and compliance with prescribed medical treatments.

Intervention follow-up

Intervention group participants received lifestyle counseling and, if the target values for BP and/or lipids (table 5) were not met in the baseline measurement, the study nurse consulted a study physician for evaluation and adjustment of pharmacological treatments. Within approximately 4 weeks after pharmacological adjustment, participants were called for a new measurement and the process repeated if necessary. All pharmacological adjustments were individualized to the needs of the patient and not restricted to any fixed algorithm or protocol. Assessments of lipid-lowering therapy were restricted to participants with ischemic stroke.

Follow-up in the control group

The control group received secondary preventive care according to local standard procedures. Secondary preventive treatment was generally initiated in-hospital. Thereafter, the patients' general practitioners (GPs) were primarily responsible for their care. Telephone contact between study nurses and control participants 1 and 12 months after hospital discharge did not include any lifestyle counseling or any adjustments to their pharmacological treatment. BP and LDL-C measurements were forwarded to the patient's GP for assessment and no further action was taken by the study team.

Table 4 Main reasons for exclusion from the randomized phase of the NAILED study.

Severe stroke
Severe heart disease
Advanced stage of other disease
Aphasia
Dementia
Impaired hearing
Participation in a concurrent clinical trial

The study nurse reported one of the given conditions as the main reason for a patient not being able to participate in the randomized phase of the NAILED study.

Table 5 Treatment targets

Measure	Target value
Blood pressure	<140/90 mmHg
LDL-C*	
Non-diabetics	<2.5 mmol/L
Diabetics†	<2.5 mmol/L or <1.8 mmol/L

*Applicable for participants with ischemic stroke. †Due to an update to the local guidelines, the LDL-C treatment target for diabetic patients changed during the course of the study. For participants with diabetes mellitus who had their 1-month follow-up after March 31, 2013, the treatment target was LDL-C <1.8 mmol/L, but it was <2.5 mmol/L for the rest of the population.

Statistics

We used the same statistical methods for descriptive statistics across all four studies. Baseline characteristics were compared using chi-square, Fischer's exact test, or the independent-samples t-test as appropriate. All tests were two-sided, and significance was determined at an alpha level of 0.05. Statistical methods specific for each study are described below.

Study I

Patients were divided into four groups depending on the year of inclusion in Riksstroke (1998-2000, 2001-2003, 2004-2006, and 2007-2009). The reference group was stratified correspondingly. The cumulative incidence of recurrent ischemic stroke was calculated using the Kaplan-Meier survival analysis with censoring for deaths. The day of admission was set as day 0. Recurrent stroke was defined as an ischemic stroke occurring from the day after discharge from the hospital until 364 days after admission. The same method was used to calculate stroke incidence in the reference population,

with the day of admission for the matched stroke case set as day 0. Comparisons were made between time periods using the log-rank test.

Multivariate Cox regression analyses were performed to identify predictors of ischemic stroke recurrence within 1 year. Only patients included during 2004-2009 were used in the regression analyses because sufficient data concerning medication at discharge were lacking for the other time periods (1998-2003). The multivariate model comprised previously established risk factors and factors found to be of potential importance in univariate analysis ($p<0.10$). Variables with >10 % missing data were excluded. The assumption of proportional hazards was verified using Kaplan-Meier curves for the individual risk factors and scaled Schoenfeld residuals. For several variables the associated risk differed significantly from the assumption of proportionality during the first 28 days after admission for the index event and the data was therefore truncated to more than 28 days.

Study II

Among identified subjects who survived through the hospital stay, we calculated the proportion that were randomized in the NAILED intervention study, the proportion that declined randomization and the proportion that were excluded from the randomized phase. Among patients excluded, we calculated the proportional distribution of reasons for exclusion. Associations between baseline characteristics and the decision not to participate in the randomized phase were analyzed using a multivariate logistic regression model including all patients eligible for inclusion and all descriptive variables found to differ significantly between randomized patients and patients declining randomization. A second multivariate model was constructed to explore the association between baseline characteristics and exclusion. This second model included all identified patients and all variables found to differ significantly between excluded patients and patients eligible for randomization. Regardless of significant differences between groups, both models also included sex as a covariate. The Kaplan-Meier method, with the log-rank test for group comparison, was used to assess the cumulative 1-year survival of randomized patients, excluded patients, and patients declining randomization. Univariate logistic regression was performed to calculate the odds ratios for mortality using the group of randomized patients as a reference category.

Study III

We used paired sample t-tests to evaluate changes in mean BP and LDL-C levels between baseline (i.e., 1 month after hospital discharge) and 12

months within a single group. We calculated the adjusted mean differences between groups (intervention vs. control) at 12 months using a general linear model adjusted for sex and the degree of disability in order to reflect the stratified randomization. A second general linear model was constructed to test the hypothesis that any difference detected between groups at 12 months may be primarily attributable to benefits affecting intervention group participants who had not reached the treatment target at baseline. In addition to accounting for sex and the degree of disability, this second model included 1) a binary indicator variable denoting participants as either above or below the target value at baseline and 2) an interaction variable between the same variable and the treatment group allocation.

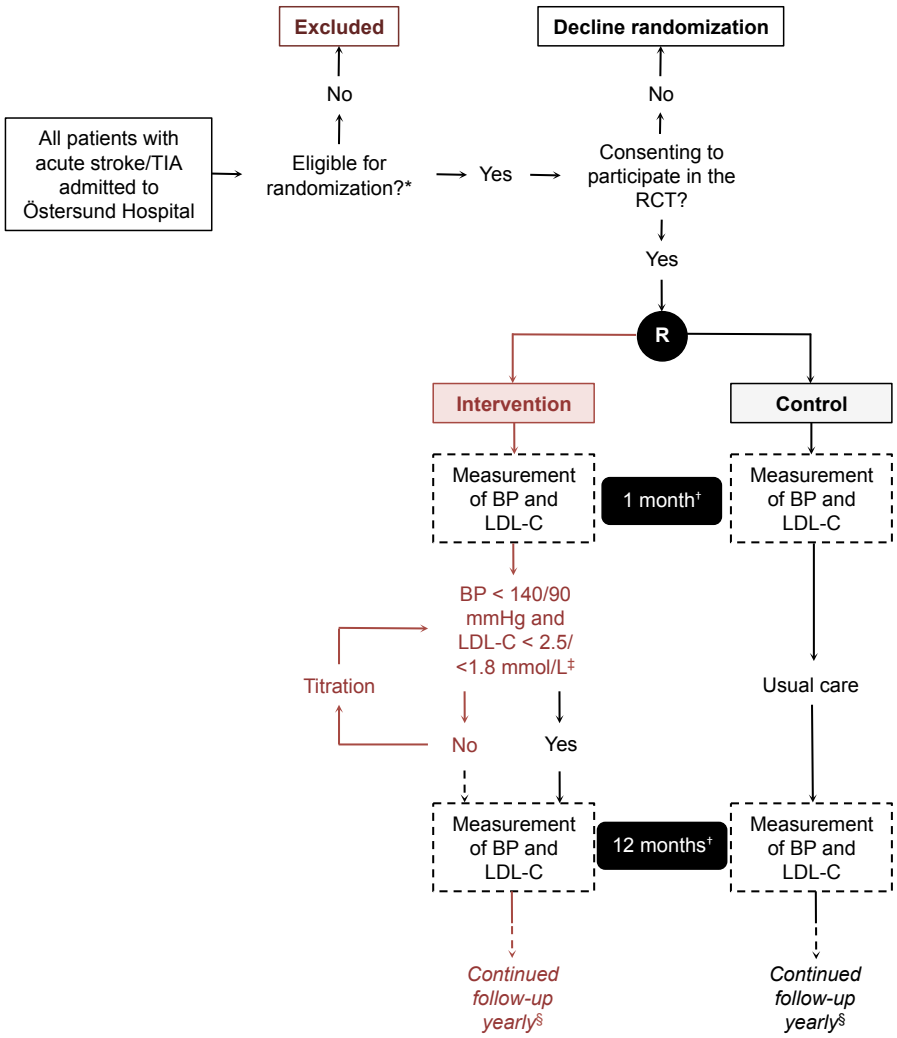
Study IV

We used a dichotomized classification of education in which we defined low education as ≤10 years of formal education (i.e., compulsory school) and high education as the completion of >10 years of formal education (i.e., upper secondary school or higher). All variables were analyzed separately for the intervention and control groups. We used the paired samples t-test to calculate the mean changes in SBP, DBP, and LDL-C between 1 and 12 months after hospital discharge. We estimated the mean differences in SBP, DBP, and LDL-C at 12 months using general linear models. The initial model included sex and baseline characteristics significantly associated with education level, and then we reduced the model to only include significant variables. As age could not be included in the models due to a high correlation with education level, we performed age-stratified analyses using a dichotomous classification of age with 70 years as the cut-off based on the population mean. Due to the low number of participants in each education group, this analysis did not include covariates.

Ethics

The Regional Ethics Committee in Umeå approved study I on August 13, 2010 (Dnr 2010-167-31M), and the NAILED study (studies II-IV) on October 28, 2009 (Dnr 09-142M). Approval to study baseline characteristics and to perform follow-up regarding mortal events among participants not included for randomization was given in two amendments to the original application (Dnr 2013-204-32M, Dnr 2014-416-32).

Figure 3 Flow of participants in the NAILED study



*Patients in a general condition permitting telephone-based follow-up according to the NAILED intervention program were considered eligible for randomization. †Time since hospital discharge. ‡LDL-C treatment target only applicable for participants with ischemic stroke. Due to an update to the local guidelines, the LDL-C treatment target for diabetic patients changed during the course of the study. For participants with diabetic mellitus who had their 1-month follow-up after March 31, 2013, the treatment target was LDL-C <1.8 mmol/L. §Follow-up was repeated at 24 and 36 months. Each of the 12, 24, and 36-month follow-up visits followed the same procedures as described for the 1-month follow-up, but only follow-up until 12 months was covered by the studies in this thesis.

Results

The 1-year risk of ischemic stroke recurrence, predictors, and temporal trends 1998-2010 (Study I)

Among 196 765 patients with an ischemic stroke registered between 1998 and 2009 (table 6), 22 198 (11.3%) patients had a recurrent ischemic stroke within 1 year after admission for the index event and 43 494 (22.1%) died. Among those who died, most did so without having experienced a new ischemic stroke (n=38 198, 19.5%). Given survival, the cumulative 1-year incidence of recurrent ischemic stroke was 13.1%.

Table 6 Baseline characteristics and treatment at discharge in the study I ischemic stroke cohort

		Missing values, n (%)
Age (years), mean (SD)	76.0 (11.4)	0
Women	98 425 (50.0)	0
Prior ischemic stroke	28 697 (14.6)	0
Prior myocardial infarction	24 248 (12.3)	0
Atrial fibrillation	52 169 (27.4)	6067 (3.1)
Diabetes mellitus*	30 568 (20.5)	1601 (1.1)
Antihypertensive drug(s) at admission*	78 809 (53.3)	2995 (2.0)
Smoking*	21 273 (16.2)	19 298 (12.8)
Thrombolysis*	3599 (2.4)	3912 (2.6)
Treatment at discharge:		
Warfarin†	16 113 (12.1)	4767 (3.5)
Antiplatelet drug(s)†	105 824 (76.7)	
ASA	87 964 (65.8)	4354 (3.2)
ASA + dipyridamole	14 734 (16.3)	47 563 (34.5)
Clopidogrel	5296 (5.9)	47 641 (34.5)
Lipid-lowering drug‡	41 213 (45.7)	3737 (4.0)
Antihypertensive drug(s)‡	67 692 (72.1)	
Calcium channel blocker	18 905 (21.0)	3824 (4.0)
Beta blocker	38 527 (42.8)	3824 (4.0)
ACE inhibitor	30 285 (33.7)	3834 (4.1)
ARB	5808 (12.6)	47 776 (50.9)
Diuretics	31 070 (34.5)	3766 (4.0)

Data are presented as n (%) unless otherwise noted. In total, the cohort consisted of 196 765 patients with ischemic stroke but several variables were not available for all four time periods and the treatment at discharge variables only refer to patients who survived through hospitalization. For the composite treatment variables ("antiplatelet drug(s)", "antihypertensive drug(s)") the proportions presented are conservative estimates of patients on treatment assuming that patients were not treated with drugs for which they had a missing value. SD, standard deviation; ASA, acetylsalicylic acid; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker. * Time periods 2000-2003, 2004-2006, and 2007-2009 (n=150 873). † Time periods 2000-2003, 2004-2006, and 2007-2009 (n=138 031). ‡ Time periods 2004-2006 and 2007-2009 (n=93 829).

Age >75 years, prior ischemic stroke, prior myocardial infarction, atrial fibrillation without warfarin treatment, diabetes mellitus, and treatment with diuretics or beta-blockers at discharge were associated with an increased risk of ischemic stroke recurrence (table 7). Warfarin treatment of atrial fibrillation, lipid-lowering medication, and treatment with acetylsalicylic acid with or without dipyridamole were associated with a decreased risk of ischemic stroke recurrence.

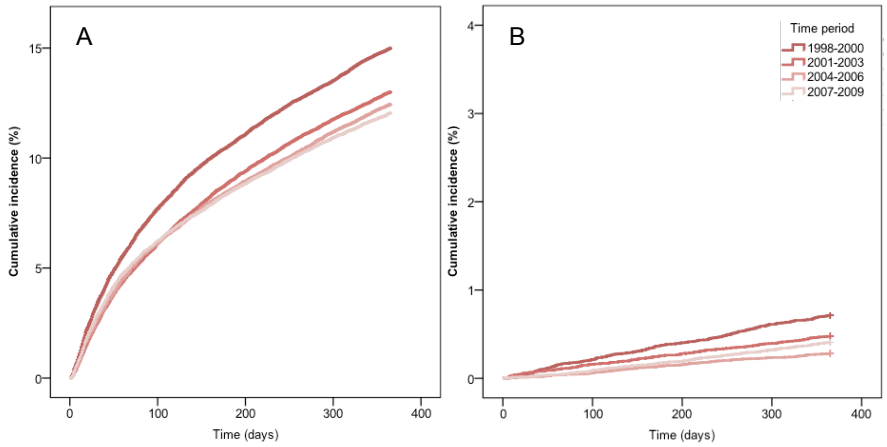
Table 7 Multivariate Cox regression analysis of factors associated with recurrent ischemic stroke within 1 year

	Hazard ratio (95% CI)
Age, years	
≤65	Ref.
66 - 75	1.04 (0.97-1.12)
76 - 85	1.13 (1.06-1.21)
≥86	1.16 (1.07-1.25)
Sex, women	0.96 (0.91-1.00)
Prior ischemic stroke	1.28 (1.20-1.37)
Prior myocardial infarction	1.26 (1.18-1.34)
Diabetes mellitus	1.18 (1.12-1.25)
AF, no warfarin at discharge	1.59 (1.50-1.68)
AF, warfarin at discharge	0.80 (0.73-0.88)
ASA	0.91 (0.85-0.97)
ASA + dipyridamole	0.85 (0.79-0.93)
Clopidogrel	1.06 (0.97-1.17)
Lipid-lowering drug	0.88 (0.84-0.93)
Calcium channel blockers	1.04 (0.98-1.09)
Beta blockers	1.21 (1.16-1.27)
Diuretics	1.07 (1.02-1.12)
ACE inhibitors	0.99 (0.95-1.04)

This analysis comprised 89 691 subjects with index events occurring from 2004 to 2009, of which 85 300 had complete data for all variables included in the model. Those who died or had a recurrent ischemic stroke during the first 28 days from admission were not included (n=12 899). CI, confidence interval; AF, atrial fibrillation; ASA, acetylsalicylic acid; ACE, angiotensin converting enzyme.

Across the four time periods, the cumulative incidence of recurrent ischemic stroke decreased by 3%, from 15.0% to 12.0% (figure 4), corresponding to a relative reduction of 20%. The age and sex distribution, the cumulative 1-year mortality and the survival curves for censored events remained similar throughout the study period. The prevalence of prior myocardial infarction and atrial fibrillation increased over time and was persistently higher among patients who had a recurrent stroke during follow-up (figure 5). Similarly, diabetes mellitus was more prevalent among patients with recurrent ischemic stroke, but the proportions were maintained during the study period. Most secondary preventive drugs were not consistently registered until 2004, but they were generally increasingly prescribed thereafter.

Figure 4 One-year cumulative incidence of A) recurrent ischemic stroke (p<0.001) in the Riksstroke cohort and B) ischemic stroke (p<0.001) in the reference population stratified by time period for the index event



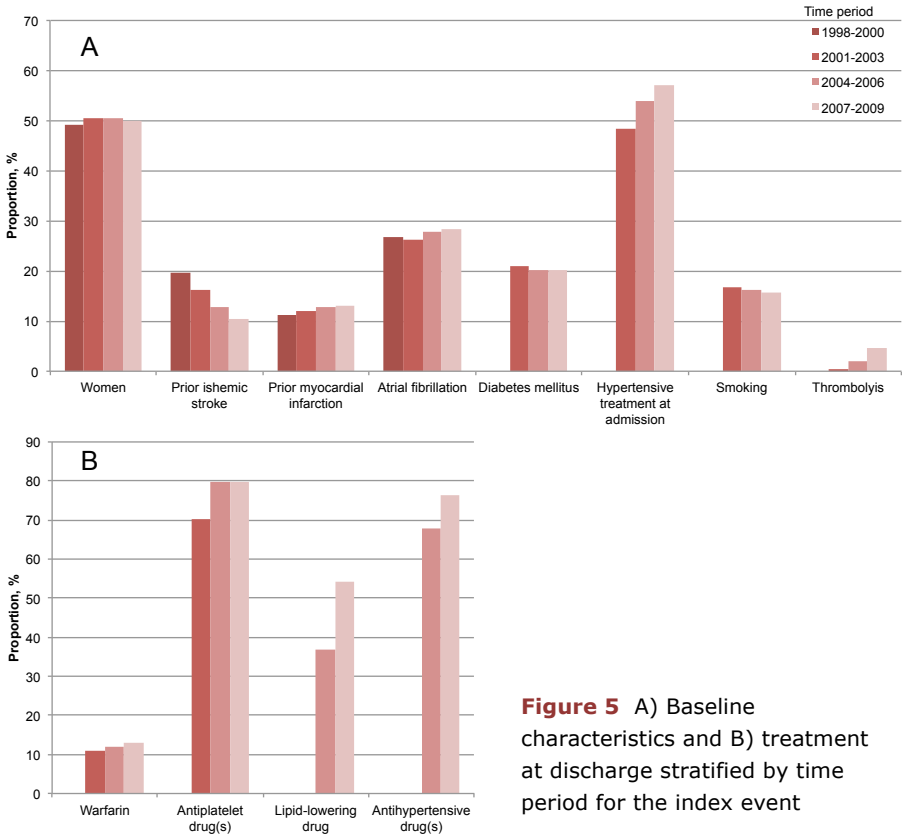


Figure 5 A) Baseline characteristics and B) treatment at discharge stratified by time period for the index event

In the reference population, 878 (0.5%) had an ischemic stroke during the year of follow-up and 11 152 (5.9%) died. From the period 1998-2000 to 2007-2009, the cumulative 1-year incidence of ischemic stroke decreased from 0.7% to 0.4%, corresponding to a RRR of 42.9%.

Nurse-led, telephone-based secondary preventive follow-up (Studies II-IV)

Overall characteristics of the NAILED population

During the 4 years of screening for the NAILED study, 1776 patients with stroke or TIA were identified (table 8). The proportion of stroke and TIA patients aged 65 years or older was 85.0% (n=1130) and 77.9% (n=348), respectively. Studies II-IV were performed in defined groups of the total NAILED population as described in the methods section.

Feasibility: Participation rate and factors associated with non-participation (Study II)

During the first 2 years of the NAILED stroke risk factor trial (January 1, 2010, until December 31, 2011), 600 patients with stroke and 287 with TIA were identified. Seventy-seven (8.7%) patients died during hospitalization. Among surviving patients (n=810), 289 (35.7%) were in a condition in which telephone-based, secondary preventive follow-up was considered to be inappropriate or not feasible (main reasons given in figure 6). These patients were excluded from the randomized phase of the NAILED study. Among remaining patients (n=521), 91 (17.5%) declined participation in the randomized phase. Overall, 430 (53.1%) of the patients who survived hospitalization entered randomization.

The group of patients excluded from the randomized phase differed substantially from the patients eligible for randomization in terms of disability, comorbidity, and burden of cardiovascular risk factors (table 9). We also identified large differences in 1-year survival, with 104 (36.0%) deaths in this group compared to 26 (5.0%) among the rest of the patients (figure 7). In a multivariate analysis, age ≥85 years, stroke (as the qualifying event compared to TIA), modified Rankin Scale >3, and congestive heart failure remained positively associated with exclusion, whereas BMI >25.0 and higher education level maintained a negative association. Patients who declined randomization differed in several ways from those who were randomized (table 9). In a multivariate analysis confined to patients eligible for randomization, only low education level remained positively associated with the decision to abstain from randomization for secondary preventive

follow-up. Among the subjects included in the multivariate analyses, 94.7% (n=767) and 97.7% (n=509) had complete data for all variables in the respective models.

Table 8 Baseline characteristics of the NAILED population by sex and qualifying event

		Sex		Qualifying event	
	All	**Men**	**Women**	**Stroke**	**TIA**
No. of subjects	1776	953 (53.7)	823 (46.3)	1329 (74.8)	447 (25.2)
Men	953 (53.7)	-	-	707 (53.2)	246 (55.0)
Women	823 (46.3)	-	-	622 (46.8)	201 (45.0)
Qualifying event					
Stroke	1329 (74.8)	707 (74.2)	622 (75.6)	-	-
Ischemic	1171 (88.1)	638 (90.2)	533 (85.7)	-	-
Hemorrhagic	155 (11.7)	68 (9.6)	87 (14.0)	-	-
Unclassified	3 (0.2)	1 (0.1)	2 (0.3)	-	-
TIA	447 (25.2)	246 (25.8)	201 (24.4)	-	-
Age, mean (SD), years	76.3 (11.5)	74.3 (11.2)	78.5 (11.4)	77.2 (11.3)	73.6 (11.5)
mRS>2	738/1773 (41.6)	343/952 (36.0)	395/821 (48.1)	698/1326 (52.6)	40 (8.9)
Current smoker	218/1718 (12.7)	127/933 (13.6)	91/785 (11.6)	163/1273 (12.8)	55/445 (12.4)
Previous smoker*	588/1718 (34.2)	393/933 (42.1)	195/785 (24.8)	430/1273 (33.8)	158/445 (35.5)
BMI, mean (SD)	26.0 (4.7) (n=1711)	26.1 (4.2) (n=924)	25.7 (5.2) (n=787)	25.8 (4.9) (n=1274)	26.3 (4.2) (n=437)
AF	485/1766 (27.5)	248/949 (26.1)	237/817 (29.0)	403/1320 (30.5)	82/446 (18.4)
IHD†	258 (14.5)	180 (18.9)	78 (9.5)	207 (15.6)	51 (11.4)
Previous stroke	299 (16.8)	160 (16.8)	139 (16.9)	250 (18.8)	49 (11.0)
Diabetes‡	374 (21.1)	229 (24.0)	145 (17.6)	299 (22.5)	75 (16.8)
CHF	172 (9.7)	84 (8.8)	88 (10.7)	148 (11.1)	24 (5.4)
PAD	51 (2.9)	29 (3.0)	22 (2.7)	46 (3.5)	5 (1.1)
Hypertension	1149 (64.7)	606 (63.6)	543 (66.0)	903 (67.9)	246 (55.0)
Hyperlipidemia§	1438/1676 (85.8)	781/917 (85.2)	657/759 (86.6)	1058/1245 (85.0)	380/431 (88.2)

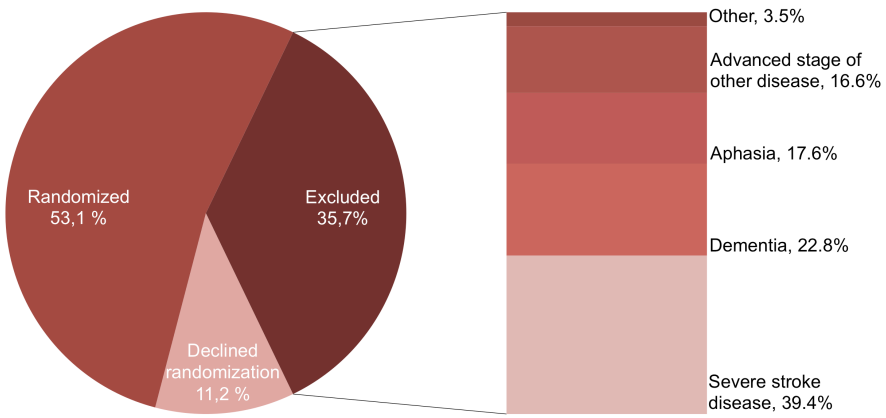
Baseline characteristics for patients identified by the NAILED study during all years of screening (2010-2013). Data are presented as N (%) unless otherwise noted. The valid denominator is given for each variable with missing values. mRS, modified Rankin Scale; BMI, body mass index (weight in kilograms/(height in meters)^2); AF, atrial fibrillation; IHD, ischemic heart disease; CHF, congestive heart failure; PAD, peripheral artery disease. *Stopped smoking >6 months ago. †Previous diagnosis of acute myocardial infarction or previous percutaneous coronary intervention or previous coronary artery bypass grafting. ‡Previous diagnosis or treatment for diabetes at discharge, § LDL≥2.5 mmol/L or total cholesterol≥4.5 at measurement during hospitalization or patient on lipid-lowering treatment at admission.

Table 9 Comparison of baseline characteristics between randomized patients, excluded patients, and patients who declined randomization

	Randomized	**Excluded**	**Declined**	p^{*}	p^{**}	p^{***}
No. of subjects	430 (53.1)	289 (35.7)	91 (11.2)			
Male	234 (54.4)	146 (50.5)	48 (52.7)	0.304	0.771	0.711
Age, mean (SD), years	71.8 (10.6)	81.5 (9.1)	77.2 (13.1)	<0.001	<0.001	0.004
Stroke	273 (63.5)	263 (91.0)	64 (70.3)	<0.001	0.215	<0.001
Ischemic	254	234	56			
Hemorrhagic	19	28	8			
Unspecified	0	1	0			
mRS >3	36 (8.4)	172 (59.5)	15 (16.5)	<0.001	0.018	<0.001
GFR (mL/min), mean (SD)	81.7 (32.1) (n=429)	60.4 (29.2) (n=281)	68.5 (34.5) (n=84)	<0.001	<0.001	0.033
BMI, mean (SD)	26.8 (4.3)	24.9 (4.9) (n=275)	25.8 (4.3) (n=84)	<0.001	0.070	0.123
Post-basic education	181/429 (42.2)	37/266 (13.9)	14/85 (16.5)	<0.001	<0.001	0.560
Ischemic heart disease	55 (12.8)	55 (19.0)	19 (20.9)	0.023	0.045	0.698
Previous stroke	73 (17.0)	89 (30.8)	24 (26.4)	<0.001	0.036	0.421
Peripheral artery disease	21 (4.9)	15 (5.2)	3 (3.3)	0.853	0.782	0.580
Congestive heart failure	21 (4.9)	52 (18.0)	8 (8.8)	<0.001	0.140	0.036
Smoking, current/prev.	206 (47.9)	94/283 (33.2)	44/90 (48.9)	<0.001	0.865	0.007
Atrial fibrillation	85/429 (19.8)	106 (36.7)	20/90 (22.2)	<0.001	0.605	0.011
Hyperlipidemia	310/323 (96.0)	210/222 (94.6)	65/69 (94.2)	0.449	0.515	1.000
Hypertension	262 (60.9)	214 (74.0)	69 (75.8)	<0.001	0.007	0.735
Diabetes	74 (17.2)	61 (21.1)	20 (22.0)	0.189	0.282	0.860

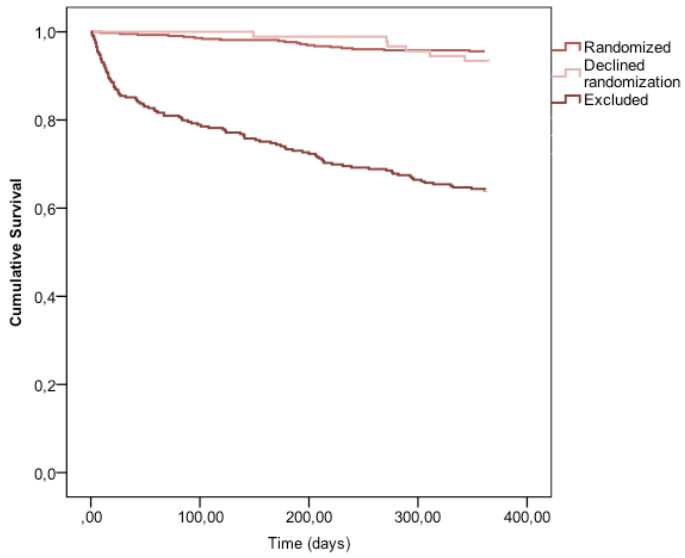
Data are presented as n (%) unless otherwise noted. *Randomized vs. excluded, **randomized vs. declined randomization, ***excluded vs. declined randomization. For variables with missing values, the valid number of cases is given for each group. mRS, modified Rankin score; GFR, glomerular filtration rate; BMI, body mass index; SD, standard deviation

Figure 6 Distribution of reasons for not participating in the randomized phase of the NAILED study



The category "others" contained non-participation due to impaired hearing or participation in another clinical trial.

Figure 7 Cumulative 1-year survival after discharge comparing randomized patients, excluded patients, and patients who declined randomization



Randomized vs. excluded: p<0.001. Randomized vs. declined randomization: p=0.213. Excluded vs. declined randomization: p<0.001.

Efficacy of nurse-led, telephone-based follow-up (Study III)

Of the 537 participants initially randomized during the first 2.5 years of the NAILED randomized controlled trial, 18 (3.4%) died, 31 (5.8%) ended their participation, and 4 (0.7%) deteriorated to a general condition preventing further participation. The loss of participants was well balanced between the two randomized groups. The remaining 484 (90.1%) participants completed the 12-month follow-up and were included in the following analysis.

The intervention and control groups did not differ in regards to baseline characteristics or BP and LDL-C values measured 1 month after hospital discharge (table 10). Overall, an equal average number of BP and/or LDL-C measures were performed in the intervention and control groups between 1 and 12 months after hospital discharge (including the 1-month measurement for both groups; table 11).

Table 10 Baseline characteristics of intervention and control group participants

	Intervention	**Control**
No. of subjects	241 (49.8)	243 (50.2)
Age, mean (SD), years	71.5 ± 11.1	70.1 ± 10.4
Women	104 (43.2)	104 (42.8)
TIA	89 (36.9)	89 (36.6)
Ischemic stroke	143 (59.3)	146 (60.1)
Intracerebral hemorrhage	9 (3.7)	8 (3.3)
mRS <3	202 (83.8)	216 (88.9)
Diabetes mellitus	40 (16.6)	46 (18.9)
Atrial fibrillation	39 (16.2)	39 (16.0)
Congestive heart failure	10 (4.1)	7 (2.9)
Previous stroke	41 (17.0)	32 (13.2)
Previous IHD	30 (12.4)	29 (11.9)
Current smoker	28 (11.6)	41 (16.9)
Antihypertensive treatment*	177 (73.4)	186 (76.5)
Lipid-lowering treatment*	191 (79.3)	193 (79.4)
Anti-platelet drug*	191 (79.3)	199 (81.9)
Warfarin*	36 (14.9)	31 (12.8)
Systolic blood pressure,* mean (SD), mmHg	137.5 (17.1)	136.9 (19.2)
Diastolic blood pressure,* mean (SD), mmHg	79.5 (10.9)	79.3 (10.5)
LDL-C,* mean (SD), mmol/L	2.5 (0.8)	2.5 (0.8)

Data are 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. SD, standard deviation; mRS, modified Rankin Scale; IHD, ischemic heart disease; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.*One months after hospital discharge.

At the 12-month follow-up, the mean SBP and diastolic blood pressure (DBP), as well as the mean LDL-C levels, had decreased in the intervention group (figure 8). In the control group, the mean BP values remained unaltered and the mean LDL-C level increased. Consequently, the mean SBP, DBP, and LDL-C values were lower in the intervention group compared to

the control group at 12 months. In addition, the proportion of patients with SBP and LDL-C values below the respective target levels was higher in the intervention group (figure 9). Among participants who had a BP or LDL-C measurement above the target value at baseline, the differences in mean SBP and LDL-C values between the intervention and control groups were more pronounced (figure 10).

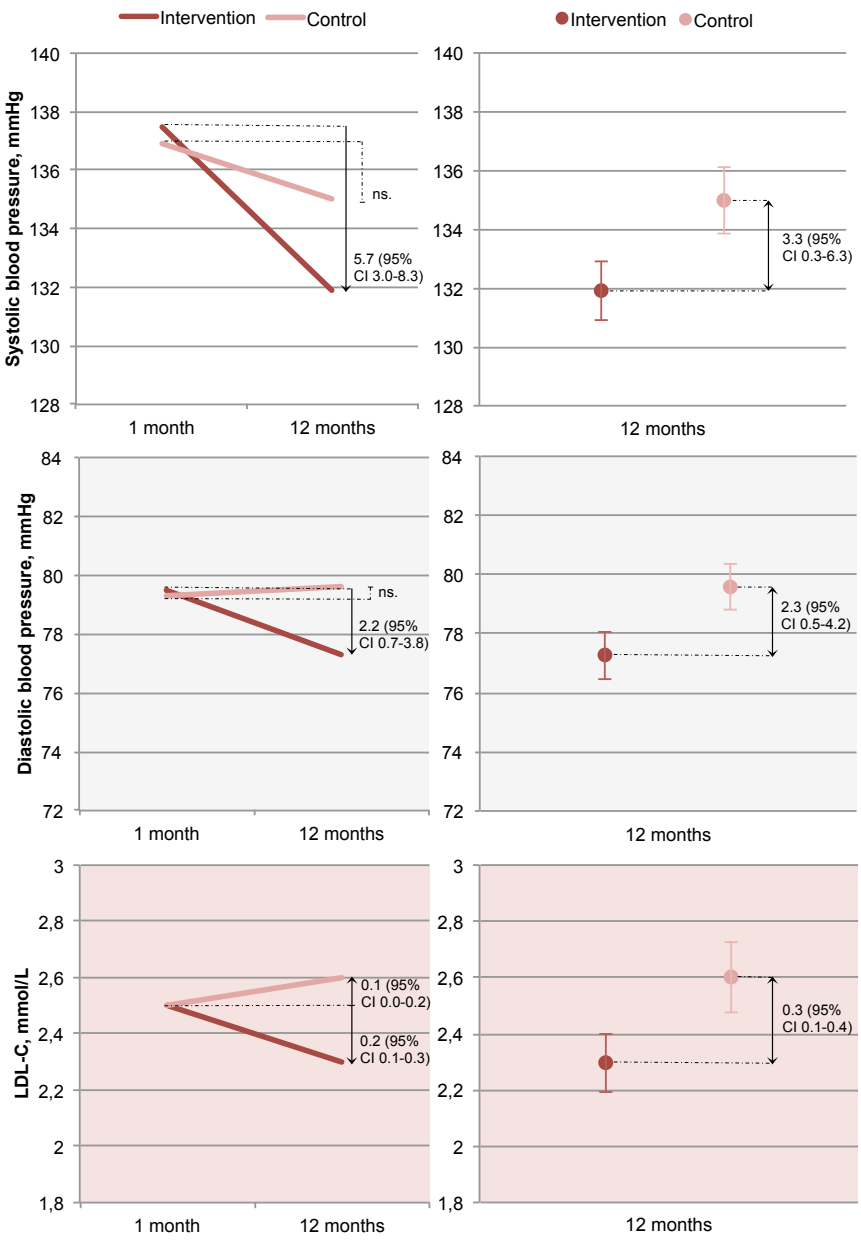
Table 11 Median number of blood pressure and/or low-density lipoprotein cholesterol evaluations from the 1-month follow-up until the 12-month follow-up

		Intervention			Control		
			BP <140/90 mmHg and LDL-C <2.5 mmol/L at baseline?			BP <140/90 mmHg and LDL-C <2.5 mmol/L at baseline?	
		All	Yes	No	All	Yes	No
In contact with a primary care center,* % (n)		97.1 (234)			95.1 (231)		
	No. of BP and/or LDL-C evaluations, median (IQR)	1.0 (0.0-2.0)	1.0 (0.0-2.0)	1.0 (0.0-2.0)	3.0 (1.0-4.0)	2.0 (1.0-3.0)	3.0 (2.0-4.0)
The NAILED study follow-up							
	No. of BP and/or LDL-C evaluations, median (IQR)	2.0 (1.0-3.0)	1.0 (1.0-1.0)	3.0 (2.0-4.0)	-	-	-

Blood pressure (BP) and low-density lipoprotein cholesterol (LDL-C) measurements documented in the patient medical record, including the measurement from the 1-month follow-up (BP measurements performed in situations of acute illness were not included). IQR, interquartile range *At least one contact with a health professional at a primary care center in addition to the measurements performed for the study.

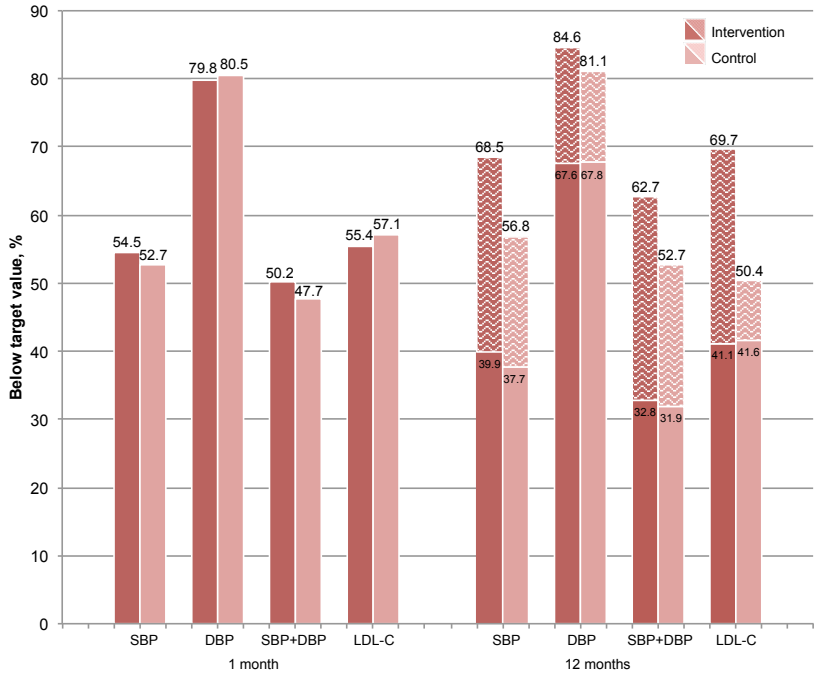
Among participants with baseline measurements below the target values, roughly one-fourth had an SBP or LDL-C measure above target values at 12 months. In addition, among participants in the intervention group who achieved the SBP (84.4%) and LDL-C (90.3%) treatment targets after intensified follow-up, roughly one-fourth had values above the target at 12 months.

Figure 8 Change in systolic blood pressure, diastolic blood pressure, and low-density lipoprotein cholesterol (LDL-C) between 1 and 12 months after hospital discharge and adjusted differences between the intervention and control groups at 12 months.



The error bars indicate standard errors.

Figure 9 Proportion of participants below the treatment target values 1 month and 12 months after hospital discharge.



The striped portion of each 12-month stack represents the proportion of patients who changed from being found above the target value at baseline to below that target at 12 months.

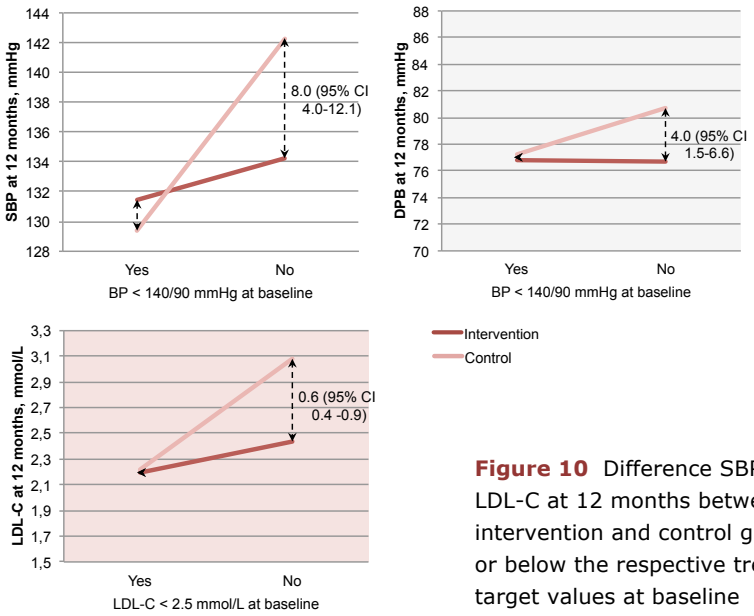


Figure 10 Difference SBP, DBP, and LDL-C at 12 months between the intervention and control groups above or below the respective treatment target values at baseline

Impact of nurse-led, telephone-based follow-up and usual care on differences in risk factor levels between education level groups (Study IV)

Roughly half of the randomized participants (50.3%, n=388) who completed the first 12 months of secondary preventive follow-up had a low level of formal education. The proportion of patients with a high level of education decreased with age for both men and women. A comparison of baseline characteristics between participants with high and low levels of education is shown in table 12. We found no significant differences in baseline SBP and LDL-C levels according to education level (table 13). At the same time point, treatment with antihypertensives was more common among participants with low education, whereas the proportions prescribed warfarin, antiplatelet drugs, or lipid-lowering agents did not differ between the two groups (table 12).

In the intervention group, SBP and DBP improved from 1 to 12 months regardless of education level, and we found no difference between the education level groups at 12 months (table 13). In the control group, mean SBP improved slightly among controls with high education, whereas the mean SBP remained unaltered among those with a low education level. Consequently, controls with low education had higher mean SBP at 12 months than controls with high education. After stratifying for age, a significant difference in SBP between the high and low education subgroups remained only for those ≤70 years of age (figure 11).

LDL-C decreased among low educated participants in the intervention group, but the opposite was observed for low educated participants in the control group (table 13). For highly educated participants, we found no alteration in LDL-C levels regardless of randomized group allocation. Among intervention group participants ≤70 years of age, LDL-C levels were lower among the low educated (figure 11). An opposite trend was observed among control group participants aged >70 years. Adjusting for sex, BMI, type of qualifying event, medical history, and functional level according to the modified Rankin Scale did not change the education level differences in SBP, DBP, and LDL-C levels at 12 months (data not shown).

Table 12 Baseline characteristics by education level

	Education level		
	High	**Low**	p-value
No. of subjects	383 (49.7)	388 (50.3)	
Age, mean (SD)	67.1(10.9)	74.3 (9.2)	<0.001
Female	151 (39.4)	166 (42.8)	0.343
Intervention group	197 (51.4)	186 (47.9)	0.331
Control group	186 (48.6)	202 (52.1)	
TIA	165 (43.1)	136 (35.1)	0.022
Stroke[*]	218 (56.9)	252 (64.9)	
mRS>2	34 (8.9)	54 (13.9)	0.028
Current smoker	53 (13.8)	53 (13.7)	0.943
BMI, mean (SD) [†]	26.7 (4.3)	27.3 (4.6)	0.045
AF	63 (16.4)	66 (17.0)	0.835
IHD	25 (6.5)	63 (16.2)	<0.001
Previous stroke[‡]	31 (8.1)	64 (16.5)	<0.001
Diabetes	47 (12.3)	81 (20.9)	0.001
CHF	8 (2.1)	20 (5.2)	0.023
PAD	10 (2.6)	12 (3.1)	0.688
Hypertension	200 (52.2)	258 (66.5)	<0.001
Antihypertensive treatment[§]	269 (70.6)	316 (81.7)	<0.001
1 drug	108 (40.1)	107 (33.9)	
2 drugs	80 (29.7)	125 (39.6)	
≥3 drugs	81 (30.1)	84 (26.6)	
Lipid-lowering treatment[§]	301 (79.0)	304 (78.6)	0.879
Simvastatin	248 (82.4)	239 (78.6)	
Atorvastatin	49 (16.3)	60 (19.7)	
Other	4 (1.3)	5 (1.6)	
Antiplatelet drug[§]	308 (80.8)	311 (80.4)	0.867
Warfarin[§]	54 (14.2)	62 (16.0)	0.475

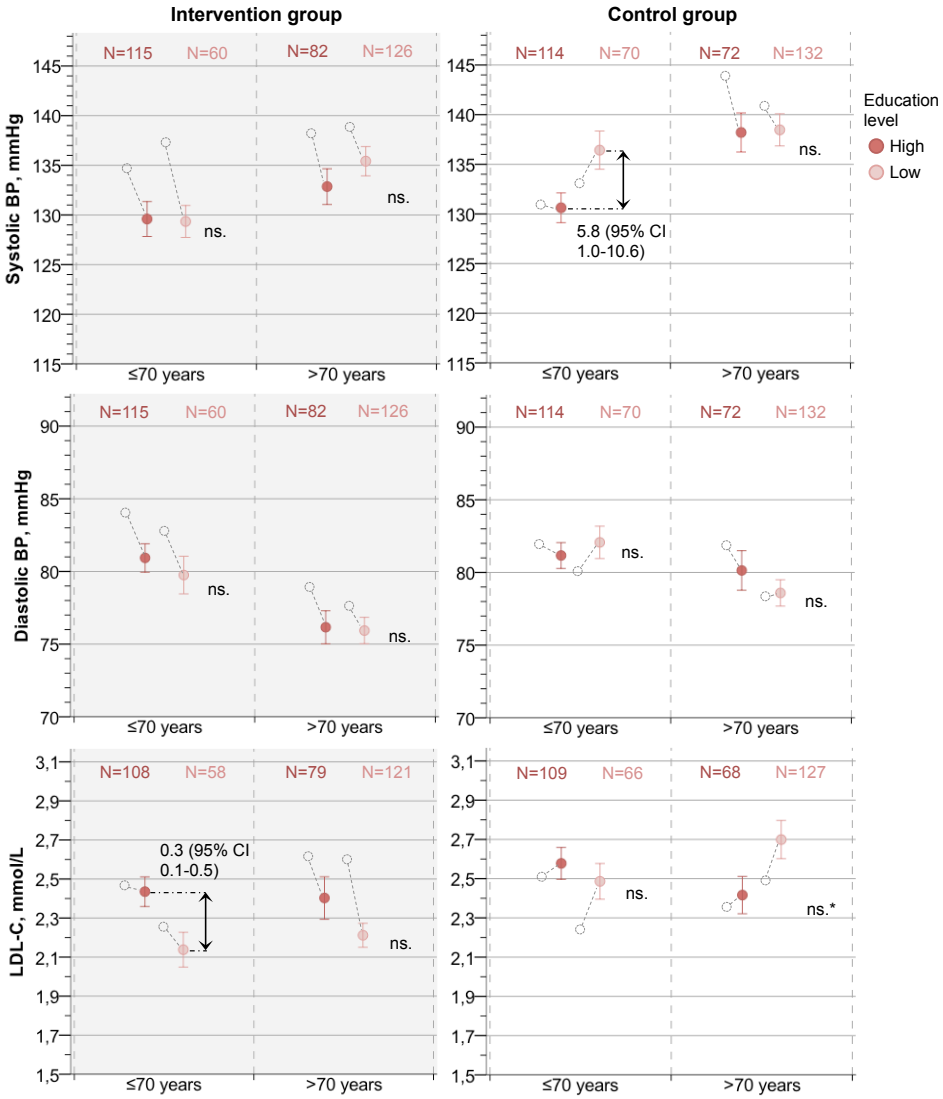
Data are presented as n (%) unless otherwise noted. mRS, modified Rankin Scale; BMI, body mass index; IHD, ischemic heart disease; CHF, congestive heart failure; PAD, peripheral artery disease; AF, atrial fibrillation; SD, standard deviation. [*] Intracerebral hemorrhage accounted for 14 (6.4%) and 9 (3.6%) of the qualifying stroke events in the highly educated and low educated groups, respectively. [†] One missing value in the high education group. [‡] Prior to the qualifying event. [§] One month after hospital discharge. There were two and one missing values from the high and low education groups, respectively.

Table 13 Association between education level and systolic blood pressure (SBP), diastolic blood pressure (DBP), and LDL-C levels.

	Intervention group Education level			**Control group** Education level		
	High	Low	Between group diff. (95% CI)	High	Low	Between group diff. (95% CI)
SBP, mmHg	N=197	N=186		N=186	N=202	
1 month*	135.9 (19.4)	138.2 (15.4)	NS	136.1 (17.9)	138.3 (19.7)	NS
12 months	130.9 (17.9)	133.5 (15.6)	NS	133.6 (16.6)	137.8 (17.7)	4.2 (0.8 to 7.6)
Change between 1 and 12 months (95% CI)	-4.9 (-2.1 to -7.8)	-4.8 (-1.9 to -7.6)		-2.5 (-0.2 to -4.8)	NS	
DBP, mmHg	N=197	N=186		N=186	N=202	
1 month*	81.8 (12.1)	79.2 (11.3)	2.6 (0.2 to 5.0)	81.9 (11.4)	78.9 (10.4)	3.0 (0.8 to 5.2)
12 months	78.9 (10.6)	77.2 (10.3)	NS	80.8 (10.3)	79.8 (10.1)	NS
Change between 1 and 12 months (95% CI)	-2.9 (-1.0 to -4.8)	-2.1 (-0.4 to -3.7)		NS	NS	
LDL-C,† mmol/L	N=190	N=182		N=179	N=197	
1 month ‡	2.5 (0.8)	2.5 (0.8)	NS	2.4 (0.8)	2.4 (0.8)	NS
12 months§	2.4 (0.9)	2.2 (0.7)	0.2 (0.1 to 0.4)	2.5 (0.8)	2.6 (1.0)	NS
Change between 1 and 12 months (95% CI)	NS	-0.3 (-0.2 to -0.4)		NS	0.2 (0.1 to 0.3)	

Data are presented as mean (SD) unless otherwise noted. SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; CI, confidence interval; NS, not significant. *In the control group, two values missing for each education level. In the intervention group, one value missing in the high education group. †The LDL-C analyses did not include participants with hemorrhagic stroke as the qualifying event. ‡ In the control group, four and two values missing in the high and low education groups, respectively. In the intervention group, one value missing in the high education group. §In the control group, two and four values missing in the high and low education groups, respectively. In the intervention group, three values missing from each education level.

Figure 11 Age-stratified association between education level and systolic blood pressure, diastolic blood pressure, and low-density lipoprotein cholesterol 12 months after hospital discharge.



The grey circles mark the BP/LDL-C levels at 1 month for each group. The error bars indicate standard error. BP, blood pressure; LDL-C, low-density lipoprotein cholesterol; ns, not significant. *Borderline significance: mean difference 0.3 mmol/L (95% CI -0.13 to 0.579, p=0.061).

Discussion

Characteristics and prognosis of the unselected stroke and TIA population

The unselected population admitted to hospital due to stroke consisted mostly of elderly patients, with ~85% being 65 years of age or older. Cardiovascular risk factors were prevalent, and a considerable proportion of the population had suffered from previous cardiovascular conditions. The TIA population was slightly younger than the stroke population, and most risk factors and comorbid or previous cardiovascular conditions were a little less prevalent than in the latter group. This is in line with previous population-based reports.[12, 19, 23, 24, 46, 48, 52, 206-208]

Most stroke patients survived the acute phase, but the risk of a new ischemic stroke event was considerable and 1-year survival poor compared to a matched reference population. It is well known that the risk of incident stroke increases steeply with age and, not surprisingly, study I showed that age also predicted stroke recurrence. Similar findings have been reported in previous studies.[36, 39, 41, 45, 47] Other factors that have commonly been described as risk factors of stroke recurrence are diabetes mellitus[38, 44, 47, 51, 54, 56] and atrial fibrillation.[44, 51, 54] Diabetes mellitus was a risk factor also in study I, but atrial fibrillation increased the risk of recurrence only if not treated with warfarin. The latter emphasizes the importance of considering treatment with oral anticoagulation for this very high-risk group. In addition, secondary preventive treatment with lipid-lowering medication and anti-platelet therapy was associated with a lower risk. This strengthened the evidence of benefits associated with these treatments outside of clinical trials, though the results should be interpreted with caution due to an obvious risk of confounding in this kind of material. This is further discussed under *Methodological considerations*.

Studying changes in the incidence of recurrent events may increase understanding of the disease and serve as a way to evaluate interventions introduced with the purpose of improving prognosis. According to the results of study I, the 1-year cumulative incidence of recurrent ischemic stroke decreased by 20% between the time periods 1998-2001 and 2007-2010, with the change appearing to be most prominent between the first two time cohorts. The relative decrease was similar in magnitude to RRRs reported by recent studies from Lombardy (Italy) and Taiwan.[50, 52] Also earlier studies have indicated decline in the 1-year risk of stroke recurrence, though these studies were often not limited to ischemic stroke events. A repeated

community-based cohort study conducted in Söderhamn, Sweden, found a decline in the 1-year recurrence between 1975-1980 and 1983-1988.[57] In Perth, Australia, a non-significant 44% relative decrease in the cumulative incidence was observed between the time periods 1989-1991 and 1995-1997.[43] In the US, the incidence rate of recurrent ischemic stroke decreased by an average of 4.5% (1994-1997 to 2000-2003) among Medicare beneficiaries aged ≥65 years.[49] Taken together, these observations indicate that several high-income countries, including Sweden, have seen a decrease in stroke recurrence spread over several decades, and that this decline has continued into the 21st century, though perhaps gradually leveling off during later years.

Insufficient risk factor control in clinical practice

Studies of cardiovascular high-risk populations in different countries have indicated that the proportion of patients who reach the treatment targets for BP and blood lipids is often suboptimal.[56, 132-135, 209] The results of study III showed that this was also the case in the NAILED population, adding to the knowledge of poor risk factor control among patients with cerebrovascular disease. Among those included in the randomized trial, approximately half had a SBP or LDL-C measure below target 1 month after hospital discharge, and among those followed in the usual care setting, the average SBP or LDL-C value had not improved after another 11 months. In the control group, the proportions reaching the BP treatment targets at 12 months were similar to the corresponding results of another Swedish RCT evaluating nurse-led follow-up after stroke.[129] Compared to data from the SEcondary Prevention after Heart Intensive care Admission (SEPHIA) registry in 2012, the proportions of patients with SBP and LDL-C values below target were considerably lower in the NAILED control group (SBP<140 mmHg: 56.8% vs. 71.1%, LDL-C<2.5: 50.4 vs. 72.1 mmol/L), but as the SEPHIA registry had an upper age limit of 75 years, the proportions are not comparable to ours.[131] In line with our results, however, the control of BP and LDL-C did not improve during the first year after discharge in any of these two studies.[129, 131] This indicates that insufficient improvement of risk factor control for cardiovascular prevention in high-risk groups is a widespread problem in Sweden, not only in the county of Jämtland.

Nurse-led, telephone-based follow-up improved blood pressure and LDL-C levels

Study III showed that nurse-led, telephone-based follow-up including titration of medication achieved better than usual care in terms of mean BP and LDL-C levels 12 months after hospital discharge. These results, which

were mediated by improvements among patients with levels above the target values at baseline, show that further optimization of modifiable risk factor levels are achievable in clinical practice, and that such improvements may be achieved through a relatively simple form of secondary preventive follow-up.

The results are in line with previous studies showing that enhancement of secondary preventive follow-up by involving nurses may be effective in reducing risk factor levels,[167, 168, 175] at least as long as adjustment of pharmacological treatment is part of the intervention. Because most previous experiences with successful programs mainly delivered by nurses were derived from populations with ischemic heart disease,[175] the NAILED study made an important contribution to the evidence for patients with cerebrovascular disease. In addition, the NAILED intervention showed that telephone-based delivery was feasible and effective. Although telephone communication has been an integrated part of follow-up in several studies,[175-177] few interventions have used it as the primary delivery method. Kerry et al. evaluated home BP monitoring with nurse-led telephone support in a stroke population with characteristics similar to ours. Although this study found no overall improvements in BP favoring the intervention, post-hoc analysis indicated a benefit comparable to our results among patients with a baseline BP>140/90 mmHg.[184]

Regarding the intensity of follow-up, the NAILED intervention was in the lower range compared to previous studies with positive results, mainly by individualizing the follow-up intensity. Patients in the intervention group had a median of 4 contacts with the study nurse, including the 1 and 12-month assessments. Among participants with a BP/LDL-C measure above the target level at 1 month, the median number of contacts was 6, though here it is worth mentioning that each measurement value above target at follow-up generally generated two contacts with the study nurse; the first contact was to give the patient feedback about measurement results and to assess adherence to treatment, and the second (after consultation with the study physician) was to give instructions regarding any adjustments in the medication. If only counting the number of BP/LDL-C measurements, which may be a more comparable way to quantify the follow-up intensity, the median number of contacts was 2 overall and 3 among those not reaching the target at baseline (excluding the 12-month assessment). In previous successful studies with stroke and TIA participants, the number of follow-up occasions ranged from 2 in 12 months[168] to monthly contacts for 5-6 months.[172, 178] In nurse-led follow-up of patients with ischemic heart disease, most interventions with positive outcomes have been rather resource demanding, involving from 7 contacts during 12 months up to as much as 18 contacts during 6 months.[175] Our results show that the overall number of

follow-up occasions can be kept relatively low by individualizing intensity. However, we noted that, although the vast majority of intervention group participants achieved the BP and LDL-C targets after intensified follow-up, roughly one-fourth had returned to levels above target values at 12 months. Similarly, approximately one-fourth of participants with values below the targets at baseline had values found above these levels at 12 months. High prevalence of visit-to-visit variability in BP has been previously described in populations with cerebrovascular disease,[71, 73] and these fluctuations seems to be an independent predictor of recurrent cardiovascular events.[71] In one study, 32-58% of patients with a normal office SBP at baseline had an average SBP≥140 mmHg in repeated measurements during the following year.[73] Taken together with our results, measurement at one occasion appears insufficient to conclude adequate BP control. Also visit-to-visit variability in LDL-C has been described and identified as an independent predictor of cardiovascular events.[210] Continued monitoring is needed regardless of baseline values, and follow-up probably needs to extend beyond 12 months to ensure that achieved values are maintained. Possible explanations underlying variability in measurements are further elaborated under *Mechanisms*.

Inequality in risk factor control between socioeconomic groups

Study IV showed that groups defined by education level did not achieve equal results regarding risk factor levels in the usual care setting, which suggests that the socioeconomic inequality in the risk of recurrent stroke could be partly explained by unequal control of risk factors in the usual care setting. In addition, the results of study IV indicate that the inequality in risk factor levels could be reduced through a relatively simple reorganization of the follow-up strategy, including an outreach approach, regular BP and blood lipid check-ups, telephone-based systematic adjustment of medication, and lifestyle counseling.

Inequality in health outcomes related to SEP has been identified as a global problem by the World Health Organization, stating that much of the total burden of disease would be avoidable if appropriate interventions to reduce the social gap were developed and implemented.[211] Cardiovascular disease is one of the major health conditions in which SEP is an important risk marker, but the effects of interventions across socioeconomic groups are seldom reported in cardiovascular disease trials[212, 213] and we are not aware of any previous study showing that a secondary preventive intervention can reduce differences in risk factor levels between socioeconomic groups. However, the Västerbotten Intervention Program (VIP) previously demonstrated that a

community-based intervention has the potential to reduce social inequality in cardiovascular and all-cause mortality on the population level. VIP applied a broad approach for cardiovascular prevention that included screening for cardiovascular risk factors and subsequent follow-up with individualized counseling and treatment for individuals with deviating values.[214, 215] Parallel to the decline in cardiovascular mortality, SBP improved gradually, with reduced differences between groups based on education level.[216] The part of the VIP that included risk factor assessment and follow-up had similarities to the NAILED intervention, though the targeted populations differed.

Notably, low education level was more common among those excluded from the NAILED trial than among those eligible for inclusion. Furthermore, low education level was more common among those who declined randomization and among those who died or left the study during the first year of follow-up. Over-representation of participants with low education among those excluded from the study is probably a reflection of worse overall health in this group, due to either a more severe stroke[60, 217] or because of other comorbidities. This may also have influenced dropouts during the course of the study. Why more patients with low education declined randomization is more difficult to answer. Lower representation of groups with low socioeconomic position is a previously recognized problem in clinical research and may represent lower motivation to participate in studies rather than a low interest in secondary prevention. There may also be clustering of other practical circumstances that affected the decision, such as more remote living or, perhaps, less social support.

Mechanisms

It is tempting to assume that the improvement in prognosis seen in study I is the result of enhanced secondary preventive treatment since the observed risk reductions in our study and the studies from Lombardy[52] and Taiwan[50] occurred alongside an increased use of secondary preventive drugs, and our multivariate analysis showed that several of these drugs were associated with a lower risk of stroke recurrence. However, such a conclusion cannot be drawn from our results, mainly due to four reasons: 1) most of the risk reduction observed in our study occurred between the first and second time period, time periods for which we lacked treatment data; 2) virtually no difference in risk was observed between the two latest time periods; 3) we did not have information regarding adherence, persistence, and BP/LDL-C levels during the year of follow-up; and 4) results associated with treatment should always be interpreted cautiously in observational studies due to inevitable confounding related to treatment decisions.

The RRR that would theoretically be expected from the increased use of secondary preventive drugs in Taiwan and Lombardy would only have accounted for a small portion of the risk reduction observed. This simple approximation, based on the rough assumption that the results of clinical trials[93, 114, 118, 123] could be directly transferred to the general stroke population, suggests that other factors played an even larger role in the observed risk reductions. Such factors could include improvements attributable to lifestyle and other components of stroke care. We did not have data on lifestyle factors during follow-up; thus, potential time trends related to such changes could not be analyzed. In the reference group of study I, stroke incidence decreased during the study period, which may reflect previously reported improvements in the prevalence and control of cardiovascular risk factors in the general population[216, 218] and high-risk groups.[130, 131] Hypothetically, these improvements could have altered the distribution of ischemic stroke subtypes and a proportional shift towards the SAO subtype could potentially have resulted in a reduced 1-year risk of stroke recurrence. Time trends in the incidence of ischemic stroke subtypes are not easily studied due to diagnostic difficulty in the subclassification of ischemic events and varying proportions classified as "undetermined". There are, however, a few reports from western European countries, which indicate that stroke due to SAO has become increasingly common. There are no corresponding reports from the Swedish population, however.

The number of patients undergoing carotid endarterectomy or carotid angioplasty and stenting increased in Sweden during the latter part of the study period but still constituted such a small portion of the total ischemic stroke population[219] that the impact on total stroke recurrence should have been negligible.

Possible mechanisms underlying the positive effect of the NAILED intervention include lifestyle-related improvements, increased adherence and persistence to antihypertensive and lipid-lowering drugs, and/or more active titration of pharmacological treatment. Although there is evidence that changes to lifestyle, including dietary patterns, weight loss, and exercise, can reduce BP and LDL-C levels,[220, 221] such changes are not easily achieved in clinical practice.[209, 222] Lifestyle-related outcome variables were not analyzed in our study, and the possible impact of lifestyle changes on the reduction of BP and LDL-C levels cannot be fully evaluated at this point. However, considering that the lifestyle intervention provided in the NAILED study was very brief (only one session at 1 month), major differences in lifestyle achievements between the two arms seem unlikely. In the primary prevention of cardiovascular disease, previous studies of low-intensity lifestyle counseling (often limited to a single session) have generally been

insufficient to significantly improve BP or LDL-C,[223] and the evidence in favor of lifestyle modification programs in patients with heart disease build on considerably more comprehensive behavioral interventions.[224] Similarly, single session lifestyle counseling has seldom been effective in secondary prevention after stroke/TIA.[129, 167, 225, 226] Interventions delivering lifestyle education and counseling on several occasions have sometimes reported significant reductions in BP among stroke and TIA patients,[169, 178, 227] but there are even more examples of studies in which no significant improvements were observed in these outcomes.[167]

Self-reported persistence to treatment is registered as part of the NAILED study but has not yet been analyzed. Therefore, we can only speculate on its potential effect in mediating improvements in BP and LDL-C levels in the intervention group. Multiple studies evaluating the effect of interventions targeting different barriers and facilitators to increase adherence to cardiovascular medications have shown that several different strategies may be effective.[228-232] The NAILED intervention targeted patient-related, condition-related, and therapy-related factors through follow-up of current medication, including answering participants' concerns about medication, explaining medical adjustments, providing feedback on medication effects by discussing BP and LDL-C measurements, reminding patients of the importance of treatment and lifestyle improvements, and encouraging adherence. The NAILED intervention had several components in common with previous interventions that had promising results regarding adherence in different hypertensive populations.[228, 233] Two RCTs evaluating the effect of repeated follow-up with patient education and behavioral change strategies found improved adherence after 3 and 6 months,[170, 234] indicating that these interventions may be effective in selected stroke and TIA populations. However, most interventions with educational and behavioral elements that target medication adherence have failed to significantly improve adherence or reduce BP/LDL-C levels in this target group,[167, 235, 236] suggesting either an insufficient effect of the intervention on medication adherence or that medication adherence is not the main barrier to improved risk factor control after stroke/TIA, at least not in a study setting in which participants may have greater adherence than the background population. Most studies measuring adherence by self-reporting may also bring uncertainty to the results. In conclusion, improved adherence and/or persistence may have contributed to the positive results of the NAILED intervention, but for now no definitive conclusions can be drawn.

In the NAILED study, the patients' GPs were provided with study measurement values for all patients in the control group. Most participants in the control group were in contact with a GP an average 3.5 times and had

their BP and/or LDL-C assessed an average of 3 times, including the 1-month study measurement. Despite this, the mean BP remained unaltered and the LDL-C level increased slightly. In the intervention group, on the other hand, most participants reached the treatment targets after titration, showing that improvement was achievable in the vast majority of patients in this population. Taken together, these results indicate the presence of therapeutic inertia in usual care and suggest that prompt titration of medication in response to measurement values above target is an essential component in achieving improved BP and LDL-C levels. As described in the *Background* section, the reasons for abstaining from treatment intensification despite elevated measurement values may be manifold, and our data do not provide evidence in favor or against any particular mechanism.

The intra-individual variability in SBP and LDL-C levels between the measurements in study III could indicate non-adherence, but there are also several other possible explanations. For example, fluctuations in BP may reflect underlying arterial stiffness as a result of atherosclerotic disease.[237] The timing of antihypertensive drug intake, pharmacodynamics characteristics, and/or differences related to the mechanisms of action for different antihypertensive agents may also play a role.[238, 239] In addition, measurement error cannot be ruled out. For LDL-C, short-term variation related to biological fluctuations and the analytical methods is expected to occur in repeated measurements, and this may also have affected the results.[240]

The results of study IV indicated that part of the insufficiency of usual care to improve risk factor levels was associated with the participants' education level. Low education was previously associated with low health literacy, and unequal achievements in usual care may be due to failure of the health care organization to compensate for disadvantages related to this concept, including lower ability to communicate and engage with health care providers, lower up-take of information regarding health recommendations,[156] and lower adherence to pharmacological treatment.[157] As indicated by the results of the NAILED intervention, important elements to overcoming such disadvantages may include an outreach approach that provides healthy lifestyle advice and systematic follow-up of risk factors and treatment to all patients.

The potential of secondary prevention

According to study II, nurse-led, telephone-based follow-up was feasible in at least 53.1% of the unselected stroke and TIA patients. Another 11.2% were

considered eligible but declined participation. Among participants included in the randomized phase, 84.4% and 90.3% in the intervention group reached the treatment targets for SBP and LDL-C, respectively, after intensified follow-up, showing that the recommended treatment targets were achievable in the vast majority of the population that could participate in this form of secondary preventive follow-up. The between-group difference in SBP (8.0 mmHg, 95% CI 4.0-12.1) among participants with levels above the treatment target was comparable to the results of previous clinical trials. In a meta-analysis of RCTs, a difference in SBP of similar magnitude was associated with a 22% RRR for recurrent stroke.[93] The corresponding difference in LDL-C (0.6 mmol/L, 95% CI 0.4-0.9) in our study was smaller than the difference reported between the treatment groups in the SPARCL trial and the clinical significance of this result more uncertain.[114]

Although the NAILED intervention was successful in reducing risk factor levels, the impact on the total burden of recurrent events could be limited, mainly due to the fact that a large proportion of the unselected population could not be reached by the intervention. Assuming that the RRR from active treatment observed in BP trials (22%) is applicable to our population, the NAILED intervention could potentially reduce the relative risk of recurrent stroke by 5% at the population level given that the intervention effect is maintained also during more long-term follow-up (calculated assuming a 22% RRR among the 24% of the unselected stroke and TIA population discharged alive, included in the randomized trial, and found to have a BP>140/90 mmHg at baseline). A lower participation rate among patients with low education levels may also negatively affect the potential to reduce inequality in the risk of stroke recurrence. It is, however, not clear as to what extent clinical trial data are transferable to the unselected stroke and TIA population, which is considerably older, has higher prevalence of comorbid conditions, a higher absolute risk of recurrent events, and higher mortality rate. The approximate gain on the population level also assumes that the risk of stroke recurrence is the same among those included in the intervention study as among those not included in the study. Whether this is the case is currently unknown. The risk of stroke recurrence may well be lower among excluded patients considering the high all-cause mortality in this group. Future long-term evaluation of the NAILED study, including assessment of recurrent cardiovascular events, will provide more clarity regarding the distribution of cardiovascular events in the unselected population.

Methodological considerations

Coverage and case validity

During the time period for study I, the coverage of Riksstroke improved gradually to reach 85% in the last year of inclusion. Validation studies performed during the early years have shown that registered patients were more often treated in stroke units than patients who were not registered,[192, 199] which suggests that the selection of patients registered in Riksstroke was systematic. Selective registration in combination with relatively poor coverage during the first years may have had a negative effect on the internal validity of study I. However, the mean age and sex distribution was similar between time cohorts and little variation was seen in in-hospital and 1-year mortality, indicating that the time cohorts were still comparable.

The IPR was chosen as the data source for identifying recurrent strokes because 1) it had relatively high sensitivity to capture hospitalized events,[203, 204] 2) there was no indication that this sensitivity should have changed over the time period studied, and 3) events could be detected already from the day after discharge. The use of IPR may, however, overestimate the true incidence because the ICD-10 allows use of the acute stroke diagnosis at readmission or transfer between health care facilities up to 12 month after the initial event.[205] We excluded diagnoses from hospitalizations at rehabilitation facilities immediately adjacent to hospitalization for the index event in order to reduce overestimation resulting from transfer between health care units. Compared to other studies that included patients within approximately the same time period, the cumulative incidence in our population was relatively high.[46, 50, 52, 54] This suggests that some overestimation probably remained. However, we did not find reason to suspect that the problem with excess registrations should have changed over time; therefore, it is reasonable to assume good validity of the time trend in stroke recurrence. Notably, other factors may have contributed to the relatively high recurrence estimates in our study. For example, the mean age in our cohort was comparably high,[30, 46, 54] and one study was selective in the registration of events occurring during the first 21 days.[46] It is also important to consider differences in cumulative incidence in relation to potential differences regarding all-cause mortality. The proportions of patients censored due to death and survival curves for such events have seldom been reported in previous studies and this makes comparison between cohorts even more difficult.

The case finding methods of the NAILED study was validated against the hospital register of diagnosis during the 3 months before the study began,

concluding that no patient with a final diagnosis of stroke or TIA had been missed during the validation period.[241] The validation was not repeated during the 4 years of inclusion, but there was no reason to believe that the proportion of patients hospitalized or undergoing acute CT should have decreased during the study period. As no independent ascertainment of diagnosis was performed as part of the study, we cannot fully evaluate the accuracy of the qualifying diagnosis. However, the resemblance of the study sample to other populations (described below) does provide indirect evidence of good internal validity.

Measurement error

Measurements of outcome variables in the NAILED study were conducted by health care professionals at different health care facilities throughout the county. Participants were provided with written instructions they were to bring to each measurement, but we cannot rule out that some measurements may not have been performed in accordance with the instructions or that measurement error may have occurred due to defective equipment or inadequate handling. Though this may have had implications for intra-individual variability, it should not have affected comparisons between randomized groups, as we can assume that any measurement errors should have been randomly distributed.

Missing data

Missing data is common in clinical research and, since it seldom occurs at random, it is a potential source of bias. In statitsical analysis, cases with missing data can either be excluded (complete case analysis) or the missing values can be substituted through different methods of imputation. We consistently used complete case analysis. In the NAILED study, the main reasons for missing outcome values was death during follow-up or active withdrawal. Although these losses were certainly systematic, the proportions were generally small and equally distributed between the intervention group and the control group. Any bias to the results due to missing values should therefore have been minor. Also in the multivariate models in study I and II, the proportions of subjects with missing data were small.

Confounding

A confounder is an external factor associated with both the outcome of interest and the studied exposure. In observational studies, outcome and exposure are affected by multiple confounders, many of which cannot be accounted for because they are not (or cannot) be measured, their

importance has not yet been discovered, or because of limitations related to the statistical methods at hand. Therefore, conclusions regarding causality can never be drawn from observational data. In study I, the associations found between different treatments and recurrent stroke should be interpreted with caution, as treatment was not randomly assigned and factors that influenced treatment decisions may also be associated with the risk of recurrence. In study II, we found an independent association between education level and exclusion. In this case, low education was most likely a marker for a poor general health condition, which made inclusion in the intervention study inappropriate or impossible. Although some would argue that the association between education and health is at least partly causal, most would agree that health is causally affected, for the most part, by other exposures that are often associated with education level, such as lifestyle-related factors, work environment, and living conditions[79] (i.e., confounding factors that we did not account for in our model). In study IV, the results may have been confounded by the fact that the education level of the general population has increased over time with gradual changes in the importance and value of education, as further discussed below.

Competing risk in survival analysis

In survival analysis, censoring refers to continuous removal of subjects who are no longer under observation. When Kaplan-Meier survival analysis is used to calculate the cumulative incidence of an event A, it is assumed that the probability of survival (=remain event-free) is equal among censored subjects as among subjects still under observation. If a subject is censored due to an event B, which precludes event A from happening, this assumption is violated and event B is called a competing risk event. Despite this assumption, Kaplan-Meier analysis is often used to study incidence of events in population where death is a frequently occurring competing risk – as in study I of this thesis. This could still be appropriate if the objective is to calculate the cumulative incidence of an event given survival, but it should be noticed that the cumulative incidence will depend on the cumulative incidence of death and that this might complicate comparison of incidences between cohorts. In study I, the survival curves for censored events (i.e deaths that happened without a preceding recurrent stroke event) were very similar between the time periods. This means that the time trend in stroke recurrence should not have been substantially affected by any time trends in competing risk.

Handling of the NAILED control group

The NAILED intervention study was an open trial, meaning that the participants and study personnel were aware of treatment allocation. This information was also available for other health care professionals through the patients' electronic medical records. Blinding is preferable in RCTs to minimize bias but is simply not possible in this kind of study for practical and ethical reasons. We cannot rule out that the study setting, to some degree, influenced the secondary preventive treatment that was given to the control group. The study team provided the GPs with BP and LDL-C values, which may not have been measured otherwise. It is also possible that patients, by participating in the study, developed a heightened awareness and became more prone to contact their GP for secondary preventive assessment and to adhere and persist to prescribed medication. Such influence on the control group would have led to an underestimation of the effect of the intervention. Hypothetically, it is also possible that some GPs abstained from adjusting treatment when they noted that the patient participated in a clinical trial, either because they were not familiar with the trial and did not want to intervene or because they thought that the patient was in the intervention group. Such impact on the control group would have overestimated the intervention effect.

Education as an indicator of socioeconomic position

Indicators used to measure inequality in health should be chosen based on the study context, as well as the hypothesis of the pathways by which the health condition in question may be affected. Lifestyle-related factors, such as smoking, diet, physical activity, and glucose metabolism, are central for the development of cardiovascular disease, and the effect of these exposures accumulate over time. In this context, education has several advantages as an indicator because it often reflects the conditions under which an individual was brought up while also often predicting future occupation, income, and related social context later in life.[84] After cardiovascular disease, or predisposing conditions such as diabetes, is established, access to and utilization of health care resources becomes increasingly important to help limit its progression and manifestations. As described previously, education is relevant also at this stage because it may affect a person's receptiveness to health education messages, communication with health care providers, and self-management. Other advantages with education are that it is also applicable to people who are not in the labor market and, as a statistical variable, it is relatively easily categorized, as progression through the education system is built on stepwise qualification through milestone achievements. The latter may enable relevant categorization in studies in

which categories have to be limited due to the sample size, which was the case in the NAILED study.

A major disadvantage of education as an indicator is that the importance and value of achieving different education milestones changes over time, which complicates the use of education in cohorts with a broad age span.[79, 84] The use of multilevel categorization for education and age-stratification are ways to increase the sensitivity of the analysis to capture associations with education level in different age groups,[84] but this requires rather large study samples. We acknowledge that the results of study IV are limited by the use of a dichotomous classification of education with the same cut-off regardless of age. The classification in our study had to be binary in order to retain statistical power and detect clinically significant between-group differences in outcomes. The education level cut-off was chosen based on few in this cohort having completed a higher level of education than upper-secondary school, and completion of a maximum of 9-10 years of school was the lowest education level category used in the NAILED study. Another education level cut-off, or perhaps stratification by occupation class, may have been more appropriate among those aged >70 years because most participants in this age group had finalized the early stages of school before the national education reform in 1962 was implemented. After this reform, a uniform and compulsory 9-year elementary school was introduced. Thus, for participants attending school after this reform, our cut-off represents the first time point at which the family needed to actively decide whether the child should continue studying. Before the education reform, the corresponding time point occurred at an earlier stage. This difference may be a contributing factor to why the study IV results differed between age groups, and it should be emphasized that our results do not rule out the existence of socioeconomic inequality in risk factor control in the older age group.

Generalizability

The NAILED study aimed to study the feasibility, implementation, and results of its intervention follow-up at the population level, i.e., in an unselected stroke and TIA population. Similarly, study I aimed to assess the risk of ischemic stroke recurrence in an unselected study population. However, both studies only included subjects evaluated at the hospital. The extent to which a hospital-based study sample is representable of the total stroke and TIA population in a defined geographic region could be questioned, as proportions referred to the hospital may vary between countries and the resulting selection bias is most likely systematic.[242] In Sweden, hospital-based stroke samples come close to being population-based, as almost all stroke patients are referred to the hospital according to

cohort studies[192, 193, 243] using case finding methods closely resembling the criteria of an ideal population-based study as defined by Sudlow and Warlow.[242] Patients not referred to the hospital are often in terminal care and, considering that few of these patients would have qualified for inclusion, it is likely that the selection by hospital referral had very limited, if any, effect on the results of the randomized trial. The results regarding the participation rate (study II) may, however, have slightly overestimated the feasibility in a completely unselected population. Some patients with symptoms of stroke or TIA may not seek acute medical evaluation at any health care facility, but that is, for natural reasons, difficult to quantify and the resulting impact on the population composition is uncertain.

The total number of first-ever stroke cases identified by the NAILED study during the 4 years of inclusion gives an approximate (unstandardized) incidence of roughly 210 per 100 000 years at risk. This is lower than the incidence found in a community-based cohort study in Örebro[17] but very similar to the national incidence estimated from hospital-based registries[198] and also similar to the incidence found in a community-based cohort study in Lund-Orup.[18] Regarding the ratio of TIA patients to stroke patients, the NAILED cohort was consistent with Riksstroke and its TIA module. The mean age, sex distribution, and prevalence of comorbid conditions and risk factors in the NAILED cohort also had great similarities with the corresponding variables in Riksstroke.[244] Given this similarity in characteristics, the result regarding the proportion of patients considered able to participate in the intervention follow-up should apply to the general stroke and TIA population admitted to hospitals in Sweden, as well as stroke and TIA populations in other countries with similar demographics, stroke epidemiology, and hospital referral pattern.

The generalizability of the results of studies III and IV depend on the organization and performance of usual care, participation rate among eligible patients, and demographics. The participation rate in the NAILED study was high; few left the study as it was being conducted and the demographics of the sampled population correspond well to the national average. As described previously, few studies have investigated the performance of usual care in terms of the control of risk factors in the secondary preventive setting. Although we cannot conclude that usual care is performed equally everywhere, the few reports that do exist imply that insufficiency of usual care to improve risk factor levels is a general problem in Sweden.[129, 131] Thus, results would most likely be reproducible also in other parts of the country.

Implication for clinical practice and future research

The results of this thesis indicate that stroke recurrence is decreasing in clinical practice, and that further reductions could potentially be achieved by enhanced secondary preventive follow-up. The NAILED study showed that a simple, but systematic and outreaching, follow-up procedure involving risk factor assessment, lifestyle advice, and adjustment of pharmacological treatment can achieve clinically significant improvements to BP and reduce LDL-C levels. The intervention was designed to be implemented in clinical practice and, considering the population-based approach, to have good generalizability, at least within Sweden. The positive intervention results seemed to be mediated in part through better achievements among the low educated. This may have implications for future organization of secondary preventive care, especially as those with low education levels are at a higher risk of stroke recurrence.

In future analyses of the NAILED study, it will be important to assess the effect of the intervention during more long-term follow-up. To increase understanding of the mechanisms underlying the intervention effect, it would also be interesting to analyze outcomes in terms of adherence to medical treatment. Finally, it remains to be shown whether this form of intervention will actually translate into reduced recurrence of cardiovascular events. Assessment of the distribution of events between the randomized population and those who were excluded from the study would be valuable for estimating the secondary preventive potential at the population level. However, the statistical power of the NAILED study sample will be limited to detecting small differences between randomized groups.

Socioeconomic differences in risk factor control have to be further studied, and the intervention effect on such differences needs to be confirmed. Future trials of interventions to improve secondary preventive follow-up and outcomes should consider the effect of the intervention across socioeconomic groups, and the representativeness of the study sample should be reported appropriately, including the participation rate in different socioeconomic groups. To increase understanding of mechanisms underlying time trends in stroke incidence and recurrence, high quality cohort studies assessing patterns regarding ischemic stroke subtypes are also needed.

Conclusions

The 1-year risk of recurrent ischemic stroke decreased in Sweden between 1998 and 2010, at least partly concurrent with increased use of secondary preventive drugs. Well-known risk factors for stroke, such as age, diabetes mellitus, previous myocardial infarction, and atrial fibrillation without treatment with warfarin, are important contributors to the risk of recurrent ischemic stroke, whereas several secondary preventive drugs are associated with a lower risk. In the population-based NAILED cohort, just over half of surviving stroke and TIA patients were included in an intervention study evaluating nurse-led, telephone-based secondary preventive follow-up. Approximately half of this sample had a BP or LDL-C level below treatment target levels 1 month after hospital discharge. Through the intervention follow-up, the BP and LDL-C levels were reduced, with increased proportions reaching treatment targets and significantly lower SBP and LDL-C levels compared to usual care 12 months after hospital discharge. When results were compared between education groups, the intervention was beneficial among participants with low education ≤70 years of age, whereas usual care seemed to disfavor this group. A large portion of the unselected stroke and TIA population was in a general condition precluding the intervention follow-up, and their prognosis in terms of 1-year mortality was poor. Patients with a low level of education were over-represented within this group and among patients declining randomization or who were lost during the first year of follow-up.

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