Timely treatment in stroke and TIA

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Abstract

In acute stroke, the effect of both acute treatments and secondary prevention is time-dependent. Patients´ delay is an important obstacle to acute recanalization therapy for stroke. To decrease this delay, a stroke educational campaign was carried out in Sweden. After an ischemic event, the risk of early recurrent stroke is particularly high if the event is caused by a carotid stenosis. Urgent carotid endarterectomy (CEA) reduce the risk of recurrent stroke, but the optimal timing for CEA after a cerebrovascular event is not known because of uncertainties with respect to the procedural risk in very urgent CEA. The aim of this thesis was to investigate the effects of the stroke campaign, and to investigate the procedural risk of very urgent CEA.

Study I, a study based on telephone interviews, evaluated public stroke knowledge and intent to call 112 before the stroke campaign. Seventy-two percent could report at least one stroke symptom and 65% indicated they would call 112 for stroke.

Study II, a study based on telephone interviews, investigated the effect of the campaign on awareness of the AKUT (equivalent to the FAST, Face-Arm-Speech-Time) test and intent to call 112. Before the campaign started, 15% had heard about the AKUT test, compared with 51% during and directly after the campaign, and 50% 21 months later. Corresponding figures were 65%, 76% and 73% for intent to call 112.

Study III, a prospective national study, evaluated the effect of the campaign on pre-hospital delay and recanalization therapy rate. During the campaign, but not the year before, nor the year after, the proportion arriving at hospital within three hours from stroke onset and the proportion receiving recanalization therapy increased significantly.

Study IV, a prospective controlled study, compared the procedural risk in patients undergoing CEA < 48 hours with CEA 2-14 days from an ischemic event. Patients undergoing CEA < 48 hours from symptom onset had a higher risk of complications (stroke and/or death) compared with those operated on later, 8.0% versus 2.9%.

In conclusion, public awareness of stroke was rather low in Sweden and was increased by the Swedish National Stroke Campaign. The campaign was also associated with a sustained increase in the proportion receiving recanalization therapy and with a small improvement of the proportion arriving at hospital within three hours. CEA < 48 hours was associated with a higher procedural risk compared with surgery 2-14 days after an ischemic event.

Keywords: stroke, transient ischemic attack, campaign, carotid artery stenosis.

Populärvetenskaplig sammanfattning på svenska

Stroke är ett samlingsnamn för hjärninfarkt (blodpropp) och hjärnblödning och är en vanlig orsak till både död och förvärvat funktionshinder. Ungefär 85% av alla stroke är orsakade av en hjärninfarkt (ischemisk stroke) och beror på att en blodpropp täppt till en av hjärnans blodkärl. Vanliga symtom på stroke är hängande mungipa, svaghet i ena armen och/eller benet samt svårigheter att tala. Symtomen debuterar plötsligt. Transitorisk ischemisk attack (TIA) är en snabbt övergående syrebrist i ett område i hjärnan. Syrebristen orsakas av en blodpropp i ett blodkärl. Blodproppen löses upp av kroppens egna proppnedbrytande system efter en kort tid. Symtomen är samma som de som uppträder vid stroke, men går över inom några minuter/timmar.

Vid stroke och TIA är behandling i tid avgörande för behandlingarnas effektivitet, både vad gäller möjliga akuta behandlingar som kan minska de skadliga effekterna av en stroke och behandlingar som syftar till att förebygga ett återinsjuknande i stroke. En stor andel patienter med stroke kommer dock för sent till sjukhus för att kunna få effektiv akutbehandling mot proppar i form av trombolys (propplösande dropp) och/eller trombektomi (mekaniskt avlägsnande av proppen). För att fler patienter med stroke skall komma till sjukhus utan onödig fördröjning genomförde Sveriges Landsting och Regioner en strokekampanj under 2011 till 2013 med syftet att öka befolkningens kunskap om stroke. Målsättningen var att lära befolkningen känna igen de vanligast strokesymtomen och öka kunskapen om vikten av att omedelbart larma 112 genom att lära ut det så kallade AKUT-testet (A-ansikte, K-kroppsdel, U-uttal och T-tid).

Hos patienter med TIA eller lindrig stroke är risken för att återinsjukna i stroke under den närmaste tiden efter det första insjuknandet hög. Särskilt hög är risken om den bakomliggande orsaken är en förträngning i halspulsådern (s.k. karotisstenos) vilket orsakas av åderförkalkning. Kirurgisk behandling av karotisstenos, i kombination med medicinering, minskar risken för återinsjuknande i stroke jämfört med enbart medicinsk

behandling. En bättre effekt erhålls om operationen görs inom de två första veckorna än om operationen utförs senare i förloppet efterföljande en stroke eller TIA. Det är dock fortsatt oklart exakt när, under dessa två veckor, det är optimalt att opereras. Med hänsyn till den höga risken att återinsjukna i stroke redan under de första dygnen, borde så tidig operation som möjligt vara att föredra. Detta förutsätter dock att komplikationsrisken vid operationen inte är högre än vid en senare utförd operation.

De två övergripande syftena med avhandlingsarbetet var (1) att undersöka effekterna av den nationella strokekampanjen med fokus på kunskap om stroke, ledtider från strokeinsjuknande till ankomst till sjukhus samt om fler fått tillgång till effektiv akutbehandling (trombolys och/eller trombektomi) och (2) att undersöka risken för komplikation med stroke och/eller död i samband med operation av karotisstenos som utförs inom 48 timmar efter symtomdebut jämfört med operation som utförs senare (48 timmar-14 dagar efter symtomdebut).

Delarbete I: Innan den nationella strokekampanjen genomfördes konstaterades via telefonintervjuer att knappt 65% uppgav att de skulle ringa 112 vid stroke. Endast 13% kunde uppger minst tre symtom på stroke medan 46% kunde uppge minst tre riskfaktorer för stroke. Män och lågutbildade hade generellt lägre kunskap om stroke. Äldre uppgav i lägre utsträckning än yngre att de skulle ringa 112, trots att de inte hade sämre kunskap om riskfaktorer eller strokesymtom.

Delarbete II: Telefonintervjuer visade att den nationella strokekampanjen har ökat befolkningens kunskap om stroke. Kunskapen ökade i alla grupper, oavsett kön, ålder och utbildningsnivå. Äldre människors kännedom om AKUT-testet och behovet att ringa 112 vid strokesymptom förbättrades dock i lägre utsträckning än medelålders och yngre personer.

Delarbete III: I denna studie fann vi att andelen som erhöll akutbehandling mot proppar (trombolys och/eller trombektomi) vid ankomst till sjukhuset ökade från 10,3% året innan kampanjen till 13,3% under kampanjens sista tolv månader. Andelen strokepatienter som kom in till sjukhus inom tre timmar från insjuknande ökade från 36,3% året innan kampanjen till 37,4% under kampanjens sista tolv månader. Såväl året före som efter kampanjen

skedde ingen ökning, vilket talar för att ökningen under kampanjen var en effekt av själva kampanjen.

Delarbete IV: Vi observerade en ökad risk för stroke och/eller död inom 30 dagar efter operation i gruppen som opererades inom 48 timmar jämfört med de som opererades 48 timmar-14 dagar efter symtomdebut (8,0% jämfört med 2,9%).

Konklusion: Innan kampanjen hade befolkningen en relativt låg kunskap om stroke. Kampanjens effekt kunde tydligast läsas av i form av en ökad kunskap om stroke i befolkningen och andelen som erhöll akutbehandling med trombolys och/eller trombektomi. Endast en marginell ökning av andelen som kom till sjukhus inom tre timmar från insjuknandet observerades. Operation av symtomgivande karotisstenos inom 48 timmar efter stroke/TIA var förenad med en ökad komplikationsfrekvens varför den förväntade nyttan med tidig kirurgi fortsättningsvis måste vägas mot den ökade operationsrisken.

List of papers

I. Nordanstig A, Jood K and Rosengren L. Public stroke awareness and intent to call 112 in Sweden. *Acta Neurol Scand. 2014; 130:400-4.*

II. Nordanstig A, Asplund K, Norrving B, Wahlgren N, Wester P, Rosengren L. Impact of the Swedish National Stroke Campaign on Stroke Awareness and Intent to Call 112 for Stroke Symptoms. *Acta Neurol Scand. 2017;136:345-51.*

III. Nordanstig A, Palaszewski B, Asplund K, Norrving B, Wahlgren N, Wester P, Jood K, Rosengren L. Evaluation of the Swedish National Stroke Campaign: a population-based time-series study. *Manuscript.*

IV. Nordanstig A, Rosengren L, Strömberg S, Österberg K, Karlsson L, Bergström G, Fekete Z, Jood K. Editor's Choice - Very Urgent Carotid Endarterectomy is Associated with an Increased Procedural Risk: The Carotid Alarm Study. *Eur J Vasc Endovasc Surg. 2017;54:278-286.*

Contents

Abbreviations

Afx	Amaurosis fugax
CEA	Carotid endarterectomy
CI	Confidence interval
CT	Computer tomography
cTIA	Crescendo TIA
ECST	European Carotid Surgery Trial
EVT	Endovascular treatment
FAST	Face-Arm-Speech-Time
HTA	Health-technology assessment
ICD	International Classification of Diseases
IVT	Intravenous thrombolysis
MRI	Magnetic resonance imaging
MRA	Magnetic resonance angiography
mRS	Modified Rankin Scale
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NIHSS	National Institutes of Health Stroke Scale
OR	Odds ratio
PET	Positron emission tomography
P-value	Level of significance
RCT	Randomized Controlled Trial
RI	Retinal infarction
SALAR	The Swedish Association of Local Authorities and Regions
SAS	Statistical Analysis Software
SD	Standard deviation
SOS-alarm	The service coordinating ambulance calls in Sweden
SPSS	Statistical Package for Social Sciences for Windows
SW-RCT	Stepped-Wedge cluster Randomized Controlled Trial
TIA	Transient Ischemic Attack
tPA	Tissue Plasminogen Activator
WHO	World Health Organization

Introduction

Stroke

Worldwide, stroke is one of the leading causes of death and disability. Globally, and in Sweden, stroke is the second most common cause of premature mortality after ischemic heart disease (1, 2). Although age-standardized rates of stroke mortality have decreased worldwide in the past two decades, the absolute number of people who have a stroke every year, and live with the consequences, or die from their stroke, are increasing due to ageing and population growth. However, there are substantial geographical differences in both stroke burden and the directions of change by country income level, with a threefold increased burden due to stroke in low-income countries compared with high-income countries. In addition, there is a much greater reduction in stroke mortality rate in high-income countries than in low-income countries (3). Rising levels of obesity and diabetes (risk factors for stroke) in many countries make this an area of major concern for global health. Thus, stroke remains one of the principal global health challenges, and its significance is likely to increase.

In Sweden about 25 000 people having a stroke every year (4, 5). This corresponds to one person having a stroke almost every twenty minutes. Stroke prevention and acute treatment that minimize the consequences of a developing stroke is therefore essential for the person at risk for having a disabling stroke as well as for the society.

Definition of stroke and stroke subtypes

The World Health Organization (WHO) defines stroke as “rapidly developing clinical signs of focal, and at times global, loss of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than vascular origin” (6).

Stroke is classified as ischemic or hemorrhagic based on the underlying pathology. For correct classification neuroimaging with either computer tomography (CT) or magnetic resonance imaging (MRI) is required. Hemorrhagic stroke arises when a blood vessel ruptures and causes an intracranial bleeding. The blood compresses and distorts the cerebral tissue, causing cell death. Hemorrhagic stroke can be either classified as intracerebral hemorrhage or subarachnoid hemorrhage based on the site of the bleeding. In ischemic stroke, a blood vessel becomes obstructed and this leads to a sudden lack of blood supply, causing focal cerebral ischemia and cell death. Stroke symptoms lasting less than 24 hours are called a transient ischemic attack (TIA). Worldwide, the incidence of ischemic stroke is twice as high as hemorrhagic stroke (7, 8), but in high-income countries such as Sweden, ischemic stroke constitutes about 85% of all strokes (9). According to a recent systematic review and meta-analysis (10), 22% of ischemic strokes are caused by an embolus from the heart, 23% by large artery atherosclerosis (such as carotid artery stenosis) and 22% by small artery occlusion. About 26% of all ischemic strokes are classified as undetermined causes. In 3% of the cases, the cause is uncommon, such as dissection, or vasculitis.

Risk factors for stroke and TIA

There are several well-known risk factors for stroke and TIA. Age is an important, non-modifiable, risk factor. From different studies, including clinical trials, prospective cohort studies, and case-control studies (11-15), we know that hypertension, smoking, obesity, unhealthy diet, physical inactivity, diabetes, heavy alcohol intake, psychological stress and depression, hyperlipidemia and cardiac causes (for example atrial fibrillation) increase the risk of stroke. The recent INTERSTROKE study (15) estimated that these ten potentially modifiable risk factors accounted for approximately 90% of all strokes. Hypertension was more strongly associated with intracerebral hemorrhage than with ischemic stroke, whereas current smoking, diabetes, apolipoproteins and cardiac causes were more strongly associated with ischemic stroke. However, hypertension is the most important modifiable risk factor for both hemorrhagic and ischemic stroke.

Time is brain in acute stroke

Understanding the mechanisms in acute stroke and why time is so important

In 1977, Astrup et al (16, 17) showed that after the onset of focal ischemia in nonhuman primate brain, measurements of electrical activity revealed regions that were dysfunctional but not yet dead. In the central areas of the stroke lesion, blood flow deficits were severe and cells died rapidly. In the peripheral areas of the stroke, blood flow deficits were milder. When Astrup et al increased the blood pressure and improved collateral blood flow, these areas recovered. Astrup et al called this brain area the penumbra, named after the astronomical term indicating areas of half-light and half-shadow (Figure 1). The penumbra referred to the areas of the brain that were damaged but not yet dead, offering the promise that if proper therapies could be instituted in time it would be possible to rescue brain tissue following a stroke (Figure 2). Since this study, penumbral science became an active area that rapidly increased our knowledge about the underlying mechanisms in brain ischemia.

A systematic review (18) of studies concerning brain ischemia has shown that for every minute delay in recanalization of a large supratentorial ischemic stroke an average of two million neurons are lost. Thus, avoiding delays to treatment will increase the number of patients with good clinical outcome. However, there is variability in the progression of penumbral regions to infarct core between individuals depending on the collateral circulation. The establishment of an infarct can take only a few minutes, but can also occur many hours later (19).

In the 1990s, it was possible to visualize the penumbra in vivo using brain positron emission tomography (PET) scanning or MRI which allowed for the identification of acute stroke patients still having a penumbra and thus receptive for restorative treatments (20-22). Further evolvements of brain imaging have since then revolutionized the diagnostics of acute stroke.

Currently, even more advanced stroke CT and MRI perfusion protocols include detailed information about the relative sizes of the infarct core and the penumbra (infarct/penumbra mismatch). Beyond providing high-resolution images of the anatomical localization and distribution of the brain infarct, such imaging techniques supply real-time dynamic information about the individual stroke pathophysiology (23).

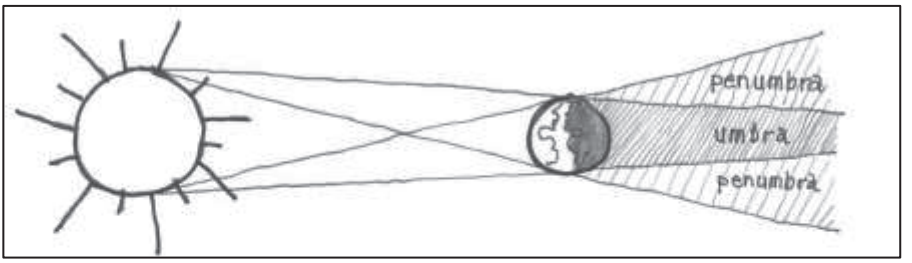

Figure 1. Penumbra, named after the astronomical term indicating areas of half-light and half-shadow.

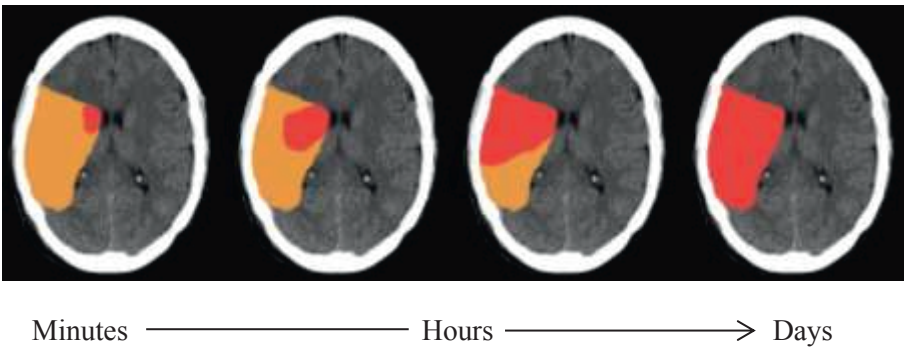

Figure 2. Illustration of the penumbra concept. The penumbra refers to the areas of the brain that are damaged but not yet dead. Orange = penumbra, red = manifest infarction.

Treatment in acute ischemic stroke

Therapeutic approaches should reflect the logical application of our present understanding of the sequence of events in the ischemic brain leading to cerebral infarction. After understanding the concept of penumbra, there was reason to believe that early treatment with restoration of the blood supply might save the ischemic tissue and improve outcome.

A milestone for stroke treatment was reached in 1996 in the USA (and 2002 in Europe), when intravenous thrombolysis (IVT) was approved for treatment of acute ischemic stroke after having been proven to increase the proportion of patients with good functional outcome in randomized trials (24, 25). A meta-analysis (26) of nine randomized trials showed that treatment within three hours from stroke onset resulted in a good functional outcome, according to modified Rankin Scale, in 33%, compared to 23% in the placebo group (OR 1.75, 95% CI 1.35-2.27). Corresponding figures for patients treated 3-4.5 hours from stroke onset, were 35% for patients treated with IVT, compared to 30% in the placebo group (OR 1.26, 95% CI 1.05-1.51). Irrespective of age and stroke severity, IVT significantly improves the odds of a good stroke outcome when given within 4.5 hours from stroke onset, with earlier treatment associated with proportionally larger benefits.

Another milestone for stroke treatment was reached in 2015, when endovascular treatment (EVT) with mechanical thrombectomy in combination with IVT was shown superior to IVT alone when treating large vessel occlusions in the supratentorial anterior circulation. The combination of EVT and IVT almost doubled the chance of good functional outcome, compared with IVT alone (27-32) when performed within six hours from stroke onset. However, progression from amendable penumbra to manifest infarction varies substantially between individuals, mainly due to differences in collateral vessel status. The inclusion of perfusion techniques (CT or MRI) in the acute stroke management algorithm allows for the identification of individual patients with large infarct/penumbra mismatch, whom can be successfully treated with EVT outside the six hours therapeutic window after symptom onset (33-35).

In acute ischemic stroke, time is brain as the time from stroke onset to revascularization of the occluded vessel is an important prognostic factor.

Therefore, the therapeutic window for any recanalization therapy (IVT and/or EVT) is narrow. Recombinant tissue Plasminogen Activator (tPA) for IVT is beneficial within the first 4.5 hours after stroke onset. However, stroke patients treated within 90 minutes after onset of symptoms show the greatest improvement, with a number needed to treat for good functional outcome (defined as symptom-free or residual symptoms with no loss of activity) of three. If tPA is started 3-4.5 hours after stroke onset, the number needed to treat is 14 (26). Although the time window for EVT is wider than for IVT, a short time from stroke onset to revascularization is the most important prognostic factor for good functional outcome, which is why treatment should be instituted as soon as possible (27-32).

The establishment of stroke care units has markedly improved the outcome for stroke patients (36). However, following the breakthrough in 1996 when the FDA first approved tPA for stroke treatment, rapid stroke diagnosis became crucial and this markedly altered the clinical management of acute stroke. Previously, clinicians often waited 12-24 hours before establishing a diagnosis of acute stroke. Thus, over a fairly short period of time, stroke has evolved into an emergent condition with effective acute treatment options. Although the proportion of patients with ischemic stroke treated with IVT and/or EVT has steadily increased over the last years, the treatment rate is still low. Only 14% of all patients registered with ischemic stroke in Sweden received recanalization therapy in 2016 (4).

Treatment in acute hemorrhagic stroke

Hemorrhagic stroke also remains a significant cause of morbidity and mortality. However, except for stroke unit care, the current therapeutic options in the acute setting remain limited. Still, early deterioration within the first few hours after stroke onset is common and can be counteracted by emergent medical treatment that under the right circumstances may have a positive impact on the outcome. For patients suffering a hemorrhagic stroke, blood pressure lowering and reversal of coagulopathy should be initiated as soon as possible. Rarely, acute neurosurgical intervention is indicated (for example in cases with cerebellar hematoma or large lobar intracerebral hemorrhages) (37).

Time is brain in secondary prevention after TIA and ischemic stroke

Early risk for stroke after TIA or minor stroke

In 2004, Coull et al (38) showed that the early risk of stroke after a TIA or a minor stroke was much higher than commonly quoted at that time. The estimated risk for stroke after a TIA was 8.0% at seven days, 11.5% at one month, and 17.3% at three months. Corresponding figures for recurrent stroke after a minor stroke were 11.5%, 15.0% and 18.5%. The risk of early recurrent stroke is highest in patients with large-artery atherosclerosis (such as carotid stenosis) compared to other subtypes (odds ratio = 3.3, 95% CI = 1.5-7.0) (39). When these studies were performed, it was unclear whether the risk could be reduced by more rapid instigation of preventive treatment (38, 39).

Secondary prevention after TIA or minor stroke

Secondary prevention starts with deciphering the most likely mechanism for the ischemic stroke or TIA. One of the main goals in stroke prevention is to treat vascular risk factors such as hypertension, diabetes and dyslipidemia. Patients should be advised to stop smoking. Changes in lifestyle such as a healthy diet, exercise and avoiding obesity should be recommended. In case of cardioembolism, most often due to atrial fibrillation, anticoagulation is the mainstay of therapy. In other common etiologies, including large artery atherosclerosis, the best medical therapy consists of antiplatelets, statins, aggressive controls of vascular risk factors, and lifestyle modifications. In patients with a symptomatic carotid stenosis, carotid endarterectomy (CEA) is highly beneficial in addition to best medical treatment (40, 41).

The effects of rapid instigation of secondary prevention

In 2004, a meta-analysis (42) showed that CEA for patients with symptomatic carotid stenosis was more favorable when done within the first two weeks after the ischemic event compared to later surgical intervention. However, these studies were not designed to determine whether surgery performed in the very early phase was even more beneficial.

Consequently, in 2007, the Early use of EXisting PREventive Strategies for Stroke study (EXPRESS study) (43) was instigated to determine the effect of very early treatment after TIA and minor stroke. Briefly, the EXPRESS study compared two different modalities of management of patients with TIA or minor stroke in a population-based prospective before versus after cohort study. Patients referred to a specialized clinic between April 2002 and September 2004 (phase one) were compared with those referred between the period of October 2004 and March 2007 (phase two). During phase two, patients received a more urgent assessment and immediate initiation of treatment. In both phases, similar treatment protocols for stroke prevention were used (including antiplatelet, antihypertensive, anticoagulation and statin therapy, as well as carotid endarterectomy when indicated), the important difference being time elapsed between symptom onset, clinic assessment and initiation of treatment. The primary outcome was recurrent stroke within 90 days of presentation. The study showed that urgent assessment and treatment reduced the 90-day risk of recurrent stroke by 80% (10.3% vs 2.1%). Although the effect of the different treatment modalities could not be separated from each other, it was unlikely that CEA contributed significantly to the reduced stroke rate due to the relatively low number of surgical interventions. Thus, this study did not add evidence to the efficiency of very early carotid endarterectomy.

Therefore, in addition to the narrow therapeutic window for recanalization therapy, it is important that patients seek medical care immediately to receive a more rapid initiation of secondary preventive treatment and thereby reduce the risk of recurrent stroke. However, although CEA should be done within 14 days, it is still not settled whether surgery within the first days is more beneficial.

Reasons for delay in acute stroke

Omitting to activate emergency services is the single most important determinant causing delay in assessment for acute stroke (44, 45). The inability of people to recognize stroke symptoms and act optimally in case of stroke explains why people delay seeking urgent care for stroke (45-47).

In 2009, a review (48) showed that the 50th percentile of the median pre-hospital delays occurred between three and four hours and the proportion arriving at hospital within three hours ranged from 6% to 92%. Inclusion criteria varied across the studies, some focusing on patients with hemorrhagic or ischemic stroke or both, and some on patients with stroke-like symptoms or with TIA. Therefore it is difficult to compare the results from these different studies. However, there was a decreasing trend over time in pre-hospital delay time, and studies including patients with stroke-like symptoms seemed to have a lower proportion of patients arriving within three hours.

Public stroke knowledge

Public knowledge about stroke symptoms, appropriate action to take if stroke is suspected and ability to name risk factors for stroke varies markedly between studies (49). Reasons for these observed differences can be attributed to overall knowledge variations between populations. However, the results are also strongly related to how the questions are formulated and how provided answers are interpreted. It is therefore difficult to directly compare the reported results from these studies. Generally, when fixed options are provided (i.e. closed questions), studies tend to indicate better knowledge than when open-ended questions are used (49). For example, the ability to name one risk factor for stroke varies from 18% to 94% between studies when using open-ended questions and from 42% to 97% when closed questions are used. Corresponding figures regarding the ability to name one correct stroke symptom were 25% to 72% when asked open-ended questions and 95% to 100% when asked closed questions. The interpretation of a given answer can also differ substantially between studies, as the predetermined options considered correct differs. For example, if “weakness” is recorded as

a correct stroke symptom, the respondents´ knowledge of weakness as a stroke symptom may be overestimated compared to studies that only accept "unilateral weakness" as a correct answer. When asked what action people would take if stroke is suspected, between 53% and 98% replied that they would call the emergency medical services (49). In the majority of studies, older persons, ethnic minority groups, those with lower levels of education and men consistently had poorer levels of stroke knowledge (49-54).

Stroke educational campaigns

Given the importance of early activation of emergency services in acute stroke as described above, it is of paramount importance to increase the proportion of individuals who take appropriate actions when experiencing or witnessing stroke symptoms. In order to potentially reach this goal, stroke educational campaigns have been suggested.

During the last decade, several mass-media campaigns targeting the general public and aiming at shortening pre-hospital delay have been conducted. In general, details of campaign design and practical execution is usually very briefly described. The degree of heterogeneity between different campaigns in terms of specific target population, duration of the intervention, main topics and messages, used media and costs, complicates comparisons between the various studies. In English-speaking countries, the FAST (Face, Arm, Speech, and Time) acronym is generally used as a mnemonic to help detect and enhance responsiveness to the needs of a person having a stroke.

The majority of the campaigns carried through have been small and local, while only a few were implemented on a national level. Examples of national campaigns directed towards the public are a campaign performed in the Czech Republic in 2006-2009 and repeated campaigns in England, Ireland and Australia.

The campaign conducted in the Czech Republic during 2006-2009 was based on donated advertising in media (radio, television, newspaper, posters, and websites) and the total cost for this campaign was estimated at 25,000 EUR per year.

In 2009, the Department of Health in England launched a national stroke campaign that has been running in cycles since then (usually one or two campaign periods per year, each running during of one to two month). It includes television, press, and radio advertisements. The overall cost of the campaign is unclear, but not insignificant. For example, the Department of Health stated that the more restricted three month advertising campaign in 2011 had a cost of about £740,000. In Ireland, the Irish Heart Foundation launched a similar national stroke awareness campaign in 2010 in order to communicate the importance of recognizing stroke symptoms and the significance of acting fast to get emergency help. As in England, the campaign has thereafter been repeated at regular intervals. In Australia, the National Stroke Foundation has run public stroke campaigns every year since 2004. In most years, the campaign period lasted for six weeks.

Evaluation of stroke campaigns

In the stroke campaign literature there are, in principal, two different main purposes when initiating a campaign. First, it may be conducted to increase stroke knowledge in the target population. Researchers following up the campaign have no influence on the campaign design itself. Secondly, a campaign may be started by a research group to test a hypothesis, e.g. if campaigns are effective or which campaign design is the most efficient. In these studies the main purpose for the campaign is to evaluate the effect of the campaign and not primarily to increase the stroke knowledge in the target population.

There are different ways to evaluate the effect of a stroke educational campaign regarding outcomes. One is to assess if the campaign increases stroke knowledge and intent to call emergency services. Another is to review actual change in behavior, such as enhanced ambulance usage, shorter time from stroke onset to emergency services contact or reduced time from stroke onset to hospital admission. Yet another path is to measure the consequences of changed behavior, such as the proportion of stroke patients receiving recanalization therapy (55).

Media companies, on the other hand, commonly evaluate a campaign impact by measuring the proportion of individuals within the target population who are reached by the message in different media. From a scientific as well as a medical perspective, such indirect surrogate variables are less valuable due to uncertainty about campaign effects in terms of more patient-oriented endpoints.

Stroke knowledge and intent to call 112

In 2014, twenty-two intervention studies and five web-based educational stroke campaigns were included in a review (56). Of the intervention studies, all (22/22) included messages about stroke symptoms and 18/22 also included messages about the need to urgently call emergency services. All but one study reported positive results in at least one item (knowledge about stroke symptoms and/or intent to call emergency services). However, in several studies only women improved (57-59). The only negative study (60) concerned a national campaign conducted in the Czech Republic 2006-2009. Only 19% had noticed the campaign. Interestingly, respondents who noticed the campaign had better knowledge than respondents who did not. This was a campaign with an extremely low budget, which may affect the ability to reach the target population. Eight of the studies in the review had a control population. None of these were national campaigns. All 22 studies were before and after studies, but 16 studies collected post-intervention data at only one time-point. The other six studies followed up the campaign effectiveness through a time interval ranging from two to six months. One study (61) collected data after a five month advertising blackout, and found that knowledge declined post-intervention.

Television proved to be the medium that yielded the most positive effects (56, 62), as it reaches many people and can be repeated several times per day for extended periods of time. Web-based campaigns are efficient in reaching a large number of people but tend to attract a selected population.

Patient behavior (patient delay, ambulance use and emergency department presentation) and consequences of behavior (recanalization therapy)

In 2015, fifteen studies were included in a systematic review (55); one randomized controlled trial (RCT), two time series analyses, eight before and after studies (three included a control group not exposed to the campaign), two retrospective observational studies, and two prospective observational studies. Thirteen studies examined pre-hospital delay, eight studies examined thrombolysis rates, five studies examined ambulance use and three studies examined emergency department presentations.

Ten studies (10/13) reported a significant reduction in pre-hospital delay times. Only three out of eight studies (3/8) showed a significantly increased proportion of patients treated with thrombolysis. Four out of five (4/5) studies reported a significant increase in the proportion of patients who arrived by ambulance. All studies (3/3) examining emergency department presentations reported some statistically significant effects, with increases in the number of emergency department presentations for stroke.

Data on long-term effects are scarce in most studies. However, studies examining emergency department presentations, pre-hospital delay and/or thrombolysis rates found that the effect declined almost immediately after the campaign (63-66), suggesting that campaigns must be repeated regularly.

How to measure the proportion reached by different media

To purchase advertisement space can be very expensive, especially television advertisement. Advertisements running during evenings are more expensive compared to daytime advertisement because more people watch television in the evenings. The more reached, the more expensive. Reach is therefore an important measure for all kinds of advertisements as it reflects the proportion in the target group that is possible to reach with different media, for example with television or printed media.

However, *reach* refers to the total number of different people exposed to a medium during a given period. Reach should not be confused with the number of people who actually consume the advertisement. It is simply the number of people who are exposed to the medium.

In Sweden, the proportion reached by television is measured by the People Meter using 1200 households representing a cross-section of households. A People Meter is an audience measurement tool used to measure the viewing habits of television audiences. The box is hooked up to the television set and has a remote control unit. Each family member in a sample household is assigned a personal "viewing button".

To measure the reach of printed media in Sweden, a professional media company (Sifo, the Swedish Institute for Opinion Surveys) commission repeated large market investigations using telephone interviews (three times each year). For both television and printed media, gross contacts in the target group can be measured. From this data the proportion reached by television and printed media, for example, at least once, at least twice and at least three times can be counted.

Number of visitors is a commonly used evaluation tool to assess the impact of digital media advertisements and estimate data traffic. Both the total number of visitors as well as the number of unique visitors is measured. To measure the numbers of unique visitors, cookies are used. A cookie is a small piece of data sent from a website and stored on the user's computer. When you visit a site, it identifies if you have the cookie. If you have this cookie, you count as a recurring visitor, otherwise a new cookie will be added and you will count as a new unique visitor. However, cookies can be deleted and more than one person can use the same computer, which is why it´s important to note that a unique visitor is not a physical single person, but rather an estimate of data traffic.

The Swedish National Stroke Campaign

The Swedish Association of Local Authorities and Regions (SALAR; an organization representing all Sweden´s municipalities, county councils and regions) developed and implemented the Swedish National Stroke Campaign. The main aim was to increase stroke knowledge and reduce delay to hospital arrival. The campaign ran between the 7th of October 2011 and the 31st of December 2013. The target audience was men and women aged 15-79 years. To sustain the gains achieved, SALAR conducted a less comprehensive follow-up campaign the year following the campaign.

The campaign used the mnemonic AKUT (a translation of the FAST acronym, where F stands for face drooping, A for arm weakness, S for slurred speech, and T for time to call 911) to develop the materials for the campaign (Figure 3). AKUT is also the Swedish word for acute.

Figure 3. Example of the advertisement.

In the first part of the campaign, the advertisements described the simple three step AKUT test and the meaning of each letter of the acronym. The latter part of the campaign focused on consolidation of stroke knowledge by, for example, depicting a person experiencing a stroke. Such advertisements also contained the AKUT message but the actual test was not described in detail and the significance of the letters was not explained.

The campaign included paid television advertisements, television spots that run on public service television, paid advertisements and banners in newspapers and social media. In addition, placards, cards, brochures and other printed materials were distributed at hospitals, outpatient clinics, worksites, sports clubs, sport events, pharmacies and health fairs. The stroke campaign also had a website (www.strokekampanjen.se) during the entire campaign and a Facebook page during the latter part. The website included information about stroke, available in fourteen different languages.

The first month of the campaign was the most cost-intensive phase. In this phase the campaign was directed to the general public. In 2012 and 2013 the campaign was less intensive than in 2011 in terms of advertising aimed for the general public. During 2012 and the first half of 2013 the campaign was primarily focused on workplaces and sport clubs rather than the general public. Activities mainly included targeted advertising in the trade press, and a less intensive advertising on television, in newspapers and via banners aimed at the general public. Printed materials were sent to over 4000 companies, communities, authorities and organizations with the purpose of activating the organization to reinforce the campaign message. Famous athletes participated in advertisements, and targeted advertising during major sports event also occurred. During the last year of the campaign social media, i.e. Facebook was used more often to promote the campaign message.

Throughout the campaign period, the professional media company that designed the campaign performed repeated market investigations. These investigations identified men and younger people as groups with lower knowledge about the AKUT test and the need to call 112.

Accordingly, during the last part (second half of 2013) of the campaign the focus was shifted towards these target groups. To achieve this, the campaign advertisements were concentrated in conjunction with TV-programs primarily aimed for this specific audience. The most intensive phases in the campaign were in October-November every year.

The Swedish county councils and regions, a part of SALAR, invested 50 million SEK, around 5.5 million EUR (2011), in the main campaign. The year following the campaign (2014), the Swedish county councils and regions conducted a less comprehensive, mainly web-based, follow-up campaign with an additional budget of 3.5 million SEK, around 0.4 million EUR (2014).

Timely secondary prevention in symptomatic carotid stenosis

As described above, the risk of early recurrent stroke is highest in TIA- and stroke patients with large artery atherosclerosis, such as carotid stenosis (39), compared to other etiological subtypes. A number of studies have reported a remarkably high risk of early stroke recurrence in patients with a TIA or minor stroke due to a > 50% carotid stenosis (NASCET criteria) (67-69). A review from 2015 estimated the stroke risk to 6.4% within the first two to three days, 19.5% at seven days and 26.1% at 14 days (70).

Carotid endarterectomy (CEA) (Figure 4), in combination with best medical therapy, is the recommended treatment for stroke prevention in patients with symptomatic stenosis of the internal carotid artery (41).

Background

Large-artery atherosclerosis, a disease in large and medium sized pre-cerebral and cerebral arteries, is considered to cause approximately 20% of all ischemic strokes. The atherosclerosis involves the parts of the arterial vessel wall that are closest to the lumen, the intima and media. Atherosclerosis leads to a thickening of the vessel wall resulting in formation of an atheroma (plaque) that narrows the lumen. The atheroma consists of lipids, inflammatory cells, and often calcifications. The atheroma has a lipid-filled core, and a protected layer of smooth-muscle cells (fibrous cap) that reduce the risk of rupture (71). However, if the fibrous cap ruptures, the lipid core gets in contact with the bloodstream which leads to platelet activation and thrombosis formation that may embolize to the brain or retina. Atherosclerosis tends to appear particularly where there is branching, tortuosity or confluence of vessels, caused by turbulence in the blood flow. However, the proportion varies by sex, age and ethnicity (72, 73). In white populations, the atherosclerotic plaques are more frequent in the extracranial arteries whereas intracranial atherosclerosis is more prevalent among the Hispanic, Asian, and black populations. In a study performed in the United States (74), 16.6% of all ischemic strokes were caused by large-artery atherosclerosis. Of these, 8.0% had an extracranial carotid stenosis, 3.5% an

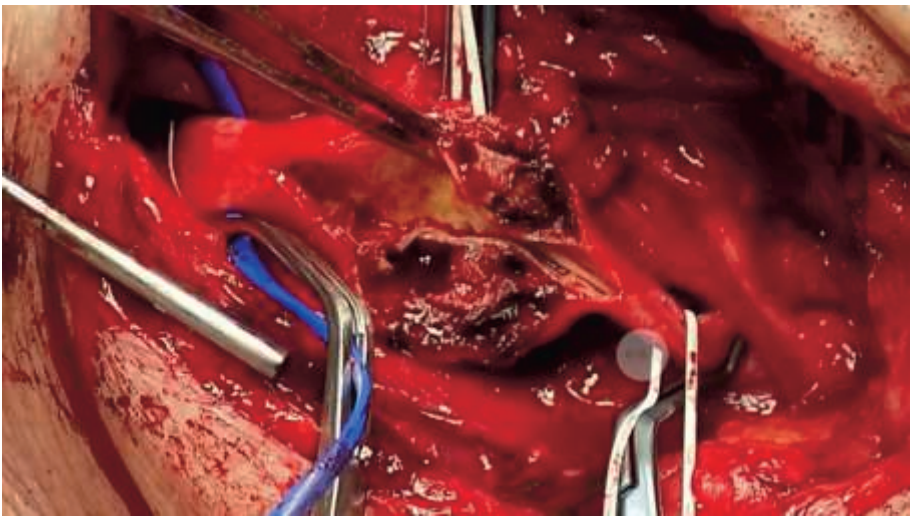

Figure 4. Carotid stenosis with an intra-plaque hemorrhage. Conventional carotid endarterectomy may be performed under local or general anesthesia. Neuromonitoring (carotid artery stump pressure or near-infrared spectroscopy) is commonly used under general anesthesia. In short, following dissection of the carotid artery bifurcation and systemic heparinization, the common and external carotid arteries are cross-clamped. If indicated by neuromonitoring, a shunt may be inserted to secure hemispheric perfusion. In the absence of shunt requirement, the internal carotid artery is subsequently cross-clamped. A longitudinal incision is made from the distal part of the common carotid artery, through the stenosis and up in to the internal carotid artery until a healthy and widely patent internal carotid artery segment is reached. The endarterectomy is thereafter carried out, removing the stenosing plaque by circumferential dissection within the natural cleavage plane located in the outer media vessel wall layer. The artery is thereafter closed, either by primary closure or by patch angioplasty depending on vessel diameter. Flow is restarted in the external- followed by the internal carotid artery. Photograph Klas Österberg.

extracranial carotid occlusion, and 3.5% had an intracranial atherosclerosis. The most common cause for associated cerebral ischemia is distal artery to artery embolization from the atherosclerotic lesion. Hemodynamic crisis due to the stenosis per se is less common. However, the most important clinical aspect of carotid stenosis is whether the stenosis is symptomatic or asymptomatic because the risk of stroke is much higher for patients with symptomatic stenosis. A carotid stenosis is classified as symptomatic if the patient has had symptoms compatible with vascular event in the anterior ipsilateral circulation.

History of carotid endarterectomy and the effects of early surgery in patients with symptomatic carotid stenosis

In 1975, DeBakey (75) published a case report about the first successful CEA for cerebrovascular insufficiency caused by atherosclerotic occlusion in the carotid artery. The surgery was performed in 1953 and the patient died from coronary occlusion 19 years after the carotid surgery.

From the middle of 1970s and the subsequent two decades the numbers of carotid endarterectomies to prevent stroke increased. In 1976, 34 000 carotid endarterectomies were performed in the United States (76). With the increased numbers of carotid surgery, more complications with strokes were observed (77). To find out if carotid surgery did more harm than good, two landmark RCTs were performed (78-80). Both studies, The North American Symptomatic Carotid Endarterectomy Trial (NASCET) (78) and The European Carotid Surgery Trial (ECST) (79), concluded that carotid endarterectomy is of proven value in stroke prevention in selected symptomatic patients with carotid stenosis. Surgery was of marginal benefit in those with 50–69% (NASCET-criteria) stenosis (absolute risk reduction of 4.6%, $p = 0.04$), and was highly beneficial in those with 70-99% stenosis (absolute risk reduction of 16.0%, $p < 0.001$) (81). Surgery was harmful in patients with a stenosis < 30%, and of no benefit in those with 30-49% stenosis. In both trials, the risk of stroke and/or death within 30 days of CEA was about 7% and did not differ between different stenosis groups.

In both trials, catheter angiography was used to define the degree of carotid stenosis and the results were expressed as a percentage reduction in vessel diameter. However, stenosis was measured differently in the two trials (Figure 5). Approximately, a 70% stenosis by the ECST method is equivalent to a 50% stenosis by the NASCET method, and an 80% stenosis by the ECST method is equivalent to a 70% stenosis by the NASCET method (82).

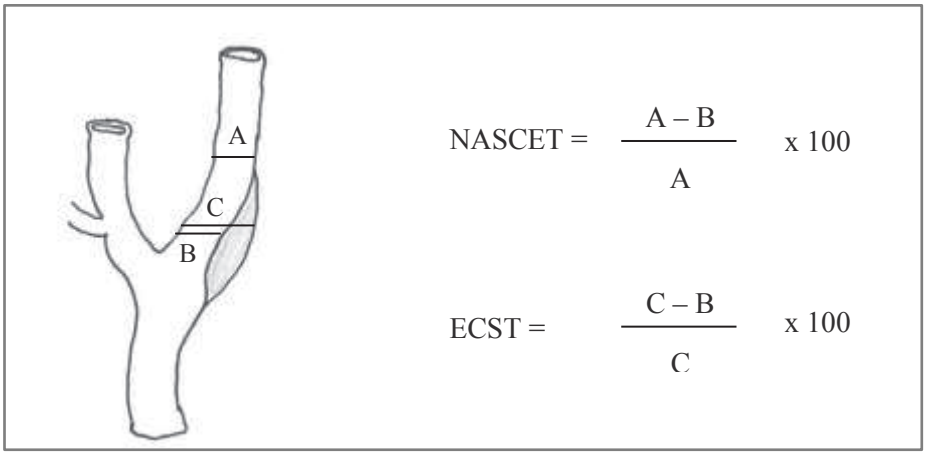

Figure 5. Two different methods for calculating degree of stenosis.

The diagnostic algorithm prior to carotid surgery has changed over the past years. Today most patients are investigated with non-invasive imaging (duplex ultrasound, magnetic resonance angiography (MRA), and/or CT angiography). Several studies showed that non-invasive methods are equivalent to angiography to investigate the degree of stenosis (83).

In 2004, a meta-analysis (42) of these two large interventional studies of symptomatic carotid stenosis showed that surgery is more favorable when done within the first two weeks after the ischemic event as compared to later surgical intervention. This result was expected as the risk of recurrent stroke in patients with symptomatic carotid stenosis is highest in the first weeks after a TIA or minor stroke. Neither NASCET, nor ECST, were designed to determine whether surgery performed in the very early phase was even more beneficial.

Benefit of CEA in different subgroups

The relative patient benefit from CEA not only depends on the degree of carotid artery stenosis and timing of CEA. Both the risk for an ipsilateral ischemic event following a TIA or minor stroke among patients with symptomatic carotid artery stenosis, and the risk for a complication (stroke and/or death) following CEA seems to be increased in patients presenting with hemispheric events (as compared to those with retinal events), in diabetic patients and in patients with irregular or ulcerated plaques (42). The perioperative risk of stroke and/or death is also higher in patients with contralateral internal carotid artery occlusion. The risk for an ischemic event following a TIA or minor stroke among patients with symptomatic carotid artery stenosis is higher in elderly people (> 75 years) explaining the greater benefit from CEA in this group (42).

Finally, in both the NASCET and the ECST trials, the rate of ipsilateral stroke in the control group was significantly higher in men, but the rate of perioperative stroke (in the interventional group) was higher in women. Consequently, it was concluded that benefit from surgery was greater in men. However, more recent data suggests that, contrary to these previous reports, women do not have a higher risk of adverse events after CEA (84, 85).

Has the benefit of CEA changed over time?

The net clinical benefit of CEA may change if the risk for an ischemic event following a TIA or minor stroke among patients with symptomatic carotid artery stenosis changes, and/or if the periprocedural risk change.

The medical treatment has evolved during the last decades. In studies from the 1990s, aspirin was the antithrombotic drug of choice and a majority of the patients were not treated with statins. Urgently instituted and more aggressive pharmacotherapy (aspirin, clopidogrel and statins) may reduce the early risk of recurrent stroke in patients with a symptomatic significant carotid stenosis (86).

In both the NASCET and the ECST, the major complication rate was about 7%. By contrast, only 3.6% of the patients who underwent CEA during the period from 2008 to 2015 in Sweden suffered a periprocedural complication (defined as any stroke and/or death within 30 days after the intervention). Furthermore, in the cohort that underwent carotid artery surgery for symptomatic carotid artery stenosis between 2014 and 2015, a significant lower major complication rate was also observed than in the corresponding patient cohort that underwent CEA 2008-2009 (87).

Thus, patient benefit from CEA may have substantially evolved over time and this remains an intriguing and complex issue.

Timing of carotid endarterectomy

The optimal timing for CEA after TIA or minor stroke remains an important and controversial issue. The risk of recurrent stroke should be balanced to the risk of per- and postoperative complications. Most guidelines, including the Swedish guidelines (37), recommend surgery within 14 days of symptom onset (88).

In the light of the high early risk for a recurrent disabling event, it is plausible to think that CEA performed in the very early period following an ischemic event could improve the benefit of CEA, if the risk of per- and postoperative complications risk remains similar, or only slightly increased, compared to later surgery. Potentially, the carotid plaques are more vulnerable immediately after an event and thus very urgent CEA may be accompanied by an increased risk for complications (89). There are no randomized studies comparing very early CEA (within 48 hours) with CEA 2-14 days after symptom onset.

In a health technology assessment (HTA) project (90) conducted at our hospital in 2009, five observational studies (91-95) reporting results of acute CEA within 48 hours after symptom onset compared with later surgery were identified. None of the studies showed significant differences in perioperative complications between the two surgery groups. However, the studies were relatively small and hampered by low external and internal validity. The years after the HTA project, several observational studies

reported on the stroke and mortality risk associated to CEA in the very early period after carotid related ischemic symptoms (96-105). In one register study (101), it was noted that patients operated within the first two days had an increased perioperative mortality and stroke risk (11.4% within two days versus 3.6% between three and seven days). However, other studies found no such differences (104, 105). A recent systematic review and meta-analysis on early carotid intervention (106) conclude that the current evidence for very early CEA is limited, and that randomized controlled trials or prospective observational studies directly comparing acute CEA with subacute surgery are needed to elucidate the optimal timing of the intervention.

Aims

The overall aim with this thesis is to generate knowledge that can improve timely acute treatment and secondary prevention in patients with acute cerebrovascular events. The specific aims were:

Study I: To investigate public stroke awareness in Sweden.

Study II: To study the impact of the Swedish National Stroke Campaign in terms of community awareness of the AKUT test (the campaign used the AKUT mnemonic: A for face drooping, K for arm/leg weakness, U for slurred speech, and T for time to call the emergency number 112) and the need to call 112.

Study III: To study the effect of the Swedish National Stroke Campaign in terms of behavior and consequences measured as delay time prior to hospital admission, and the proportion of ischemic stroke patients (< 80 years) receiving early recanalization therapy.

Study IV: To test the hypothesis that very early (within 48 hours) CEA in patients with symptomatic carotid stenosis would not increase the risk of per- or postoperative complications compared to CEA performed during the later period (48 hours to 14 days) after an ipsilateral cerebrovascular event.

Subjects and Methods

Study Design

The study design of the four studies is summarized in Table 1. There are two studies based on telephone interviews, one register based study and one prospective controlled study.

Study	Design	Participants	Source	Aims
I	Descriptive study, based on telephone interviews	Randomly selected from the national phone number register, n =1500	A national phone number register	Evaluate public knowledge of stroke symptoms, risk factors and intent to call 112 for stroke symptoms
II	Before, during and after study, based on telephone interviews	Randomly selected from the national phone number register, n =11 913	A national phone number register	Evaluate the effect of the national campaign on public awareness of the AKUT test and the need to call 112
III	Prospective national cohort study, a register study	Patients registered in Riksstroke 2010-2014, n=97 840	Riksstroke, Statistics Sweden	Evaluate the effect of the national campaign on the proportion arriving at hospital <3 h from stroke onset and the proportion receiving recanalization therapy
IV	Prospective controlled study	Patients with symptomatic carotid stenosis, n=418	Consecutive regional hospital data	Compare the procedural risk of CEA performed <48 h vs CEA 48 h-14 d following an ischemic event.

Table 1. Overview of studies included in the thesis. CEA = Carotid endarterectomy. The AKUT test is a translation of the FAST acronym (F - face drooping, A - arm weakness, S - for slurred speech, and T- time).

Subjects

Study I and II

The potential participants were randomly selected from a national phone number register of representative population samples of adults aged 18 to 79 years from all of Sweden. The register includes fixed telephone networks, mobile phones and internet protocol telephony. About 75-80% of the Swedish population of age 18-79 years is registered in the register.

Study III

Patients presenting with acute stroke between October 1, 2010, and December 31, 2014, and who were recorded in the Swedish national quality register for stroke care (Riksstroke), were included in the study. Patients already enrolled at the hospital at the stroke onset were excluded.

Study IV

The two centers that perform CEA in the Region Västra Götaland in the South West of Sweden participated. Recruitment of consecutive consenting patients started at the Sahlgrenska University Hospital in October 2010 and at the second center Södra Älvsborg Hospital in June 2012. Recruitment continued until December 2015.

Patients with symptoms compatible with a thromboembolic event in the anterior circulation, an ipsilateral carotid stenosis of 50-99% (NASCET criteria), and carotid surgery within 14 days after an ischemic event were eligible for the study. Except for the contraindications used in clinical praxis for CEA within 14 days (such as major stroke and patients with severe life-limiting disease), patients treated with intravenous thrombolysis due to the ischemic event were excluded.

Methods

Study I-II, based on telephone interviews

A professional telephone interviewing company (www.indikator.org) was commissioned by the SALAR to conduct a random digit dial telephone survey by interviewing 1500 residents before, three times during, directly after and nine, 13 and 21 months after the campaign (i.e. at eight different time-points), see Figure 6. At least six attempts were made to complete unanswered calls. Call attempts were done at different days of the week and at different times of the day. When connecting, the interviewers asked for the holder of the dialed telephone number. Number of completed interviews, dropouts and reasons for dropouts were registered.

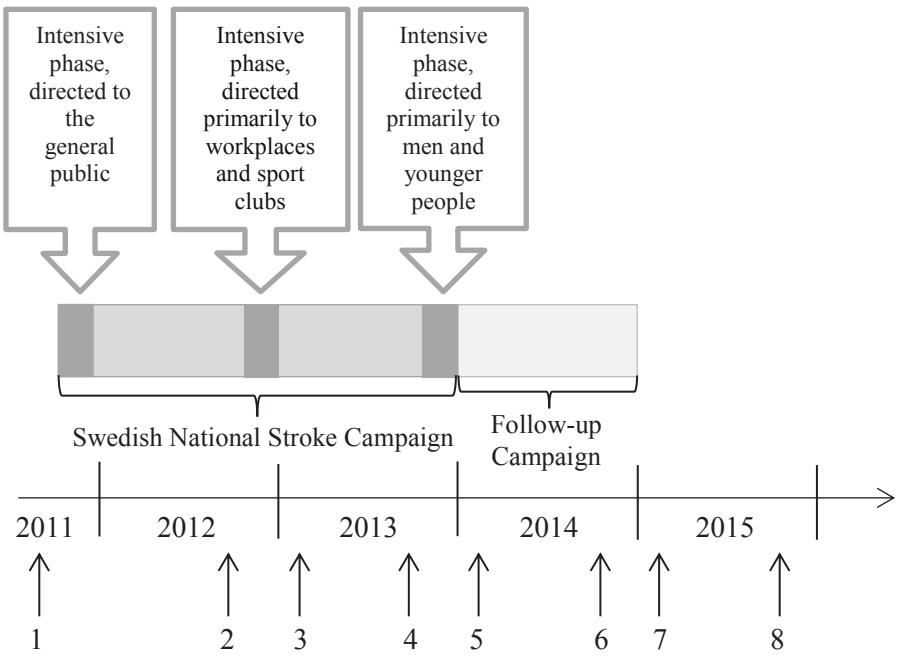

Figure 6. Timing of the telephone surveys.

Open-ended questions were used to identify sources of stroke information. The respondents were asked to name up to three different sources. Respondents were also asked if they remembered seeing advertisements regarding stroke during the latest months, and those who answered yes were given a second open-ended question to determine where they had seen it (answers were categorized as: television, newspaper, digital, other). Respondents were asked what they would do if they witnessed someone having a stroke, or if they themselves experienced sudden stroke symptoms. Predefined acceptable answer patterns considered as intent to call 112 (except the actual answer "call 112") were the responses "call SOS" and "call an ambulance" in combination with the response "112" to the subsequent query about which phone number to use in order to activate such emergency services.

Open-ended questions were used to assess the knowledge of the AKUT test. They were asked if they ever had heard about the AKUT test, and if they could state the significance of each letter. The respondents were then asked to name up to three symptoms for stroke. The options predetermined to be considered as correct were difficulty understanding or slurred speech, trouble walking/dizziness/loss of balance, unilateral numbness, unilateral weakness, headache and vision problems. The survey also included questions about demographics, such as highest level of education, marital status and country of birth.

The questionnaire used for surveys 1-6 included open-ended questions to assess the respondents´ general knowledge about risk factors for stroke. The respondents were asked to name up to three risk factors. Predefined answer options considered as correct were smoking, hypertension, heart/ cardiovascular disease, diabetes, high serum cholesterol, heredity for stroke/TIA, psychological stress, lack of physical activity, alcohol overconsumption, unhealthy diet, obesity, depression, high intake of sodium chloride and high age. Surveys 1-6 also included questions about previous diagnoses constituting personal risk factors for stroke. This specific part of the questionnaire was excluded for surveys 7-8, as the contribution from these questions was considered negligible during this last part of the follow-up assessments.

Study III, a register based study

The variables used to measure campaign effects on behavior and consequences were (1) proportion arriving at hospital within three hours from stroke onset and (2) proportion receiving recanalization therapy. The registers below were used for collecting data to study III. Data from the registers was linked through patients´ unique personal identity number.

Riksstroke:
The Swedish Stroke Register, Riksstroke, was established in 1994 to monitor, support, and improve the quality of stroke care in Sweden. All hospitals admitting acute stroke patients in Sweden participate (72 hospitals in 2017). Coverage was calculated at 90.5%, based on comparisons with the routine hospital discharge register. Validations show considerable over diagnosis of acute stroke in routine clinical practice. Allowing for this, the Riksstroke coverage is 96.5% (2010) (107). The register includes information about age, sex, stroke subtype, living conditions prior to stroke, time for stroke onset, time for arrival to the hospital, recanalization therapy data and level of consciousness upon admission at the hospital.

Statistics Sweden (The Total Population Register):
The Total Population Register is maintained by Statistics Sweden and is the basis for all official population statistics. Since 1969, this register has been the base register for the official Population Statistics and is updated daily with data on population changes from The Swedish Tax Agency. For the purpose of our study, information about educational level, country of birth, and community size were obtained from this register.

Study IV, a prospective controlled study

A neurologist examined the patients before, two and 30 days after carotid surgery. Data was prospectively documented in electronic case record forms and compiled in a predefined database. Doppler ultrasound scanning was used to assess the degree of carotid artery stenosis. Brain CT was performed in all patients with cerebral hemisphere TIA or stroke (i.e. all patients except those with retinal ischemia) in order to rule out hemorrhage and other differential diagnoses. In addition, patients with stroke underwent Diffusion Weighted MRI to rule out large-sized infarcts not suitable for early carotid surgery (Figure 7).

To reduce selection bias, a fast track for patients with recent symptoms was introduced with the purpose to enable CEA within 48 hours for all patients seeking care within 24 hours. Patients considered eligible were investigated with carotid Doppler ultrasound within two hours (daytime). If a symptomatic significant carotid stenosis was found, the investigation was supplemented with acute neuro-imaging, which was deemed necessary in order to facilitate a fast treatment decision.

The primary endpoint was the composite of death and/or any stroke within 30 days of the surgical procedure. Secondary outcomes were any stroke, ipsilateral stroke and ischemic ipsilateral stroke within 30 days of the surgical procedure (Figure 7).

Study IV, power and sample size

With a power of 80%, a 6% increase of complications measured as primary outcome could be detected with a total of 600 patients, and 150 patients undergoing CEA within 48 hours ($p < 0.05$). During study planning, we estimated that about 35 patients annually would undergo CEA within 48 hours after the ischemic event, rendering a study duration of 4-5 years.

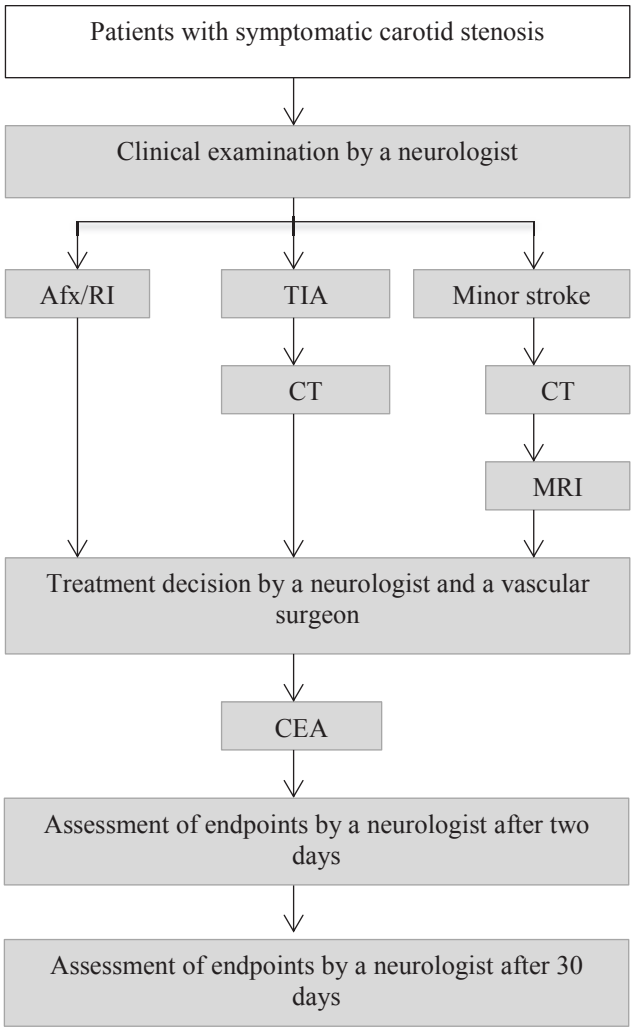

Figure 7: Diagnostic work-up. TIA = transient ischemic attack; Afx = amaurosis fugax; RI = retinal infarction; CT = computed tomography; MRI = magnetic resonance imaging; CEA = carotid endarterectomy.

Statistics

Descriptive statistics are presented as frequencies or mean values and standard deviations. For comparison between groups Student´s t-test or Fisher´s Exact test was used for dichotomous variables, the Mantel-Haenszel Chi Square test for ordered categorical variables, the Chi Square test for non-ordered categorical variables, and the Mann-Whitney U-test for continuous variables. Odds ratio (OR) were calculated using logistic regression analyses and are expressed as OR with 95% confidence intervals (CI) and/or with p-values. All p-values are two-tailed and $p < 0.05$ was regarded as significant.

In study I, multivariable logistic regression analysis was used to identify independent factors associated to knowledge of $\geq$ 3 symptoms, $\geq$ 3 risk factors for stroke, and intent to call 112. Variables included in the multivariable models were selected by univariable analysis at $p < 0.05$.

In study II, multivariable logistic regression analysis was used to investigate the campaign effect on knowledge of the AKUT test, and intent to call 112. Variables included in the multivariable models were selected by univariable analysis at $p < 0.05$ plus predefined possible confounders (sex, age and education).

In study III, multivariable logistic regression analysis was used to investigate the campaign effect on the proportion of patients arriving at hospital within three hours from stroke onset and the proportion receiving recanalization therapy. Variables included in the multivariable models were predefined possible confounders (age, sex, education, country of birth, community size, living alone at stroke onset, previous stroke, ADL-independent before stroke onset, living in an institution before stroke onset, level of consciousness and for arrival at hospital within three hours also stroke subtype).

In study IV, for the primary endpoint, variables with $p < 0.1$ in the univariable logistic regression analyses were included in a multivariable model.

Interaction analysis was used in study II to investigate factors associated with increased improvement during the study period. In study III Cochran-Armitage test for trend was used to test the significance in trends.

In study I and II, SAS 9.2 (SAS Institute Inc., Cary, NC, USA) was used for the statistical analyses. In study III and IV the Statistical Package for Social Sciences for Windows (SPSS, Armonk, NY, USA) was used for statistical analyses, version 22.0 in study III and version 23.0 in study IV.

Ethical approvals

The effect of the Swedish National Stroke Campaign was followed up by information from registers and telephone interviews. The register-study (study III) was approved by the regional ethical board of Gothenburg (reference number 551-12). SALAR commissioned a professional telephone interviewing company to carry out the telephone interviews, as a part of the campaign, to continuously evaluate the campaign effect. Some of the results have been presented previously in Swedish media. The data from the interviews was primarily collected in a database and did not included data that could identify a person (no unique personal identity number or date of birth). The called telephone number was not registered and there was no existing code list that could identify the person after the interview. Data were saved totally anonymized. The research group had access to the material as a third part, without handling any personal data in the research project. Ethical vetting was therefore judged not to be applicable for this specific part of the project. In the Carotid Alarm Study (study IV), written informed consent was obtained from all participants. The regional ethical board of Gothenburg approved the study (reference number 567-09).

Results

Study I

The response rate was 62%. Reasons for not completing the interview were: the telephone interview was refused (26%), the recipient proved unavailable despite multiple callbacks during the study period (10%), language barriers (1%), and illness (1%). Compared with the Swedish resident population aged 18-79 years, respondents were more likely to be older and born in Sweden.

Intent to call 112 for stroke symptoms

Less than two-thirds (65%) indicated that they would call 112 if they witnessed or experienced stroke symptoms. Intent to call 112 was found to be poorer in men and those with lower levels of education. Increased age was associated with a significantly lower intent to call 112 for stroke symptoms (Figure 8 and Table 2).

Seventy-two percent of those who could name at least three stroke symptoms reported that they would call 112 compared to 60% of those with no correct responses ($p < 0.001$). However, of those who reported intent to call 112 for stroke symptoms, 26% were unable to report any correct stroke symptom.

Knowledge about stroke symptoms

The most commonly reported stroke symptom was difficulty with understanding or slurred speech (reported by 39% of the participants), followed by unilateral numbness and unilateral weakness, both reported by 22%. Seventy-two percent could correctly report at least one, 43% at least two, and 13% three or more stroke symptoms. Similar to intent to call 112, men and those with lower levels of education had poorer knowledge of stroke symptoms (Figure 8 and Table 2).

Knowledge about risk factors

Smoking, reported by 40%, was the most commonly known risk factor followed by psychological stress (30%) and hypertension (28%). Overall, 86% named at least one correct risk factor, 69% at least two, and 46% correctly listed three or more risk factors. Also for stroke risk factors, men and those with lower levels of education showed poorer knowledge (Figure 8 and Table 2).

Respondents with self-reported risk factor(s) did not indicate more correct risk factors or stroke symptoms than those without. However, they were more likely to name their own risk factor as a stroke risk factor.

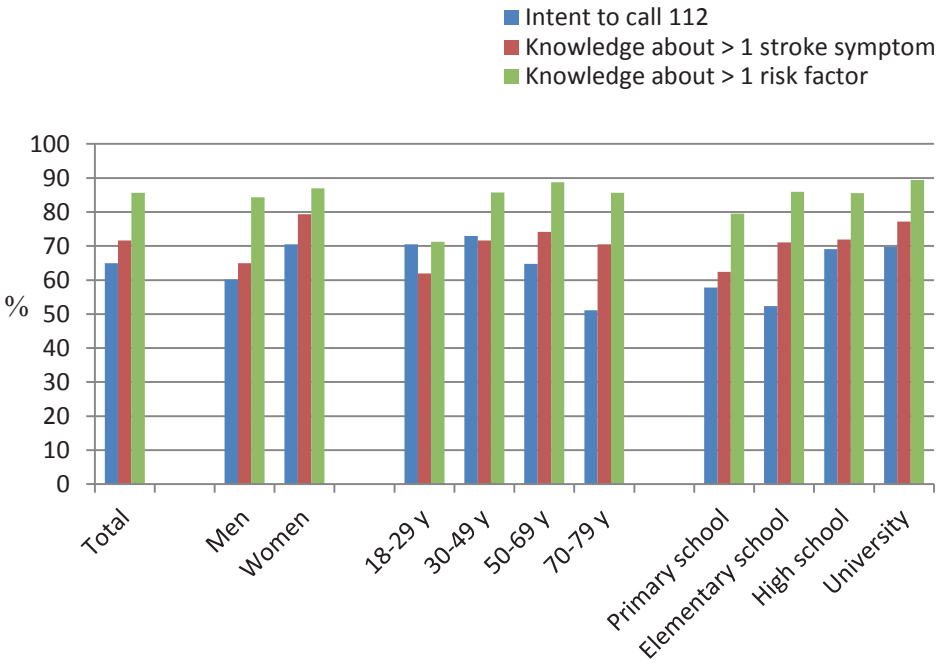

Figure 8. Intent to call 112, knowledge about stroke symptoms and knowledge about risk factors, over all, by sex, age and level of education (%). N = 1443.

Factor	Univariable logistic regression analysis		Multivariable logistic regression analysis	
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Intent to call 112				
Age, per year	0.98 (0.97–0.99)	< .0001	0.99 (0.98–0.99)	0.0002
Female	1.59 (1.27–1.98)	< .0001	1.48 (1.18–1.85)	0.0007
Education				
Primary school	1.00		1.00	
Elementary school	0.80 (0.54–1.21)	0.2907	0.79 (0.52–1.99)	0.2545
High school	1.63 (1.20–2.23)	0.0018	1.28 (0.92–1.78)	0.1504
University	1.68 (1.23–2.30)	0.0012	1.40 (1.01–1.93)	0.0434
Knowledge of ≥ 3 stroke symptoms				
Age, per year	1.00 (0.99–1.01)	0.5503		
Female	1.82 (1.34–2.48)	0.0001	1.79 (1.30–2.45)	0.0003
Education				
Primary school	1.00		1.00	
Elementary school	2.06 (1.10–3.87)	0.0245	2.14 (1.14–4.03)	0.0187
High school	1.43 (0.85–2.41)	0.1777	1.37 (0.81–2.31)	0.2413
University	2.46 (1.49-4.07)	0.0004	2.30 (1.38-3.80)	0.0013
Knowledge of ≥ 3 risk factors				
Age, per year	1.00 (1.00–1.01)	0.1928		
Female	1.37 (1.11–1.69)	0.0030	1.29 (1.04–1.60)	0.0207
Education				
Primary school	1.00		1.00	
Elementary school	1.74 (1.14–2.64)	0.0098	1.71 (1.12–2.61)	0.0127
High school	1.91 (1.39–2.61)	< .0001	1.83 (1.33–2.52)	0.0002
University	2.96 (2.15–4.08)	< .0001	2.80 (2.03–3.86)	< .0001

Table 2. Univariable and multivariable logistic regression analysis; factors associated with intent to call 112, knowledge of ≥ 3 stroke symptoms and knowledge of ≥ 3 risk factors for stroke (n=1443).

Study II

Compared with the Swedish resident population aged 18-79 years, respondents were more likely to be older and born in Sweden. During the study period, the response rate declined gradually from 62% to 36%, mainly because of an increased proportion of people not available despite multiple callbacks (Figure 9).

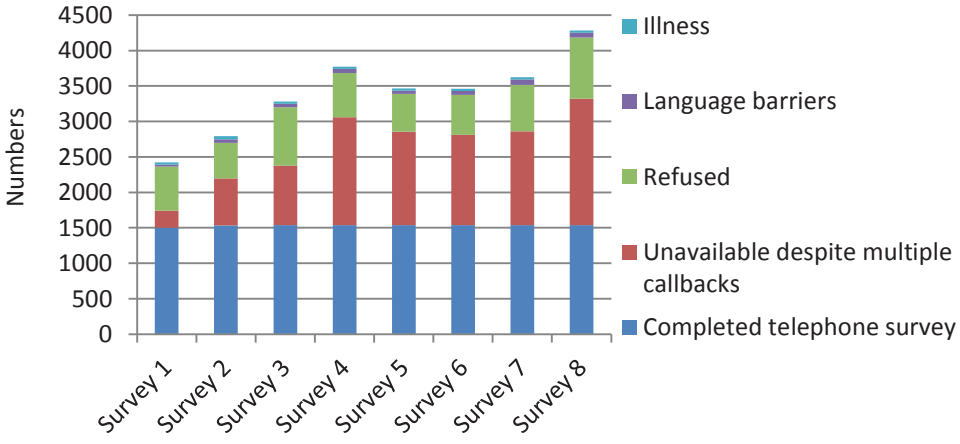

Figure 9. Completed interviews, and reasons for not completing the interviews (numbers).

Campaign exposure

Before the campaign started, 28% of the respondents reported that they had noticed recent stroke advertisements, compared to 52% during the campaign. Television was the most frequently reported source of advertisement.

The AKUT test

Before the campaign started, 15% of the respondents had heard about the AKUT test. During and directly after the campaign the proportion increased to 51%. By 21 months post-campaign, the proportion that had heard of the AKUT test remained unchanged at around 50% (Table 3). The proportion of respondents who had heard about the AKUT test increased in all subgroups (i.e. sex, age, and educational level). However, knowledge about the AKUT test was consistently higher among women and respondents with higher levels of education (Figure 10 and 11). Relative improvement during the course of the campaign was independent of sex and educational level. By contrast, we found that older individuals' knowledge of the AKUT test improved less (Figure 12).

Before the campaign started, 4% could recall the meaning of some or all keywords in the AKUT test, compared with 23% during and directly after the campaign, and 14% 21 months later.

Impact on intent to call 112

Intent to call 112 when experiencing or observing a potential stroke increased from 65% pre-campaign to 76% during and directly after the campaign. By 21 months after the campaign, intent to call 112 was 73% (Table 3). Compared with during and directly after the campaign, the proportion that indicated intent to call 112 was slightly but significantly lower at 21 months after the campaign; 76% vs. 73% (OR 0.87; 95% CI 0.76-0.99). Similar to the AKUT test, intent to call 112 increased in all subgroups (i.e. sex, age and education level) during the campaign, and intent to call 112 remained consistently higher among women and respondents with higher levels of education. Also in line with the effects on the AKUT test, the relative improvement for intent to call 112 was independent of sex and educational level, but dependent on age as we found that older individuals improved less (Figure 12).

Variable	Before the campaign n=1443	21 months after the campaign n=1518	OR (95% CI)	Adjusted OR (95% CI)[a]
AKUT test				
Have heard about the AKUT test	213 (15%)	753 (50%)	1.28 (1.25-1.31)	1.30 (1.26-1.33)
Can recall all keywords in the AKUT test	4 (0.3%)	35 (2%)	1.36 (1.17-1.57)	1.34 (1.15-1.55)
Can recall some/all keywords in the AKUT test	55 (4%)	220 (14%)	1.23 (1.18-1.29)	1.23 (1.17-1.28)
112				
Intent to call 112	937 (65%)	1109 (73%)	1.06 (1.03-1.08)	1.05 (1.03-1.08)

Table 3. Stroke awareness (the AKUT test) and intent to call 112 pre-intervention compared with 21 months after the end of the campaign. Odds ratios (ORs) and adjusted ORs were calculated using logistic regression analysis. [a]Adjusted for sex, age, education, smoking, diabetes, relative that has had a stroke, physical inactivity and overweight.

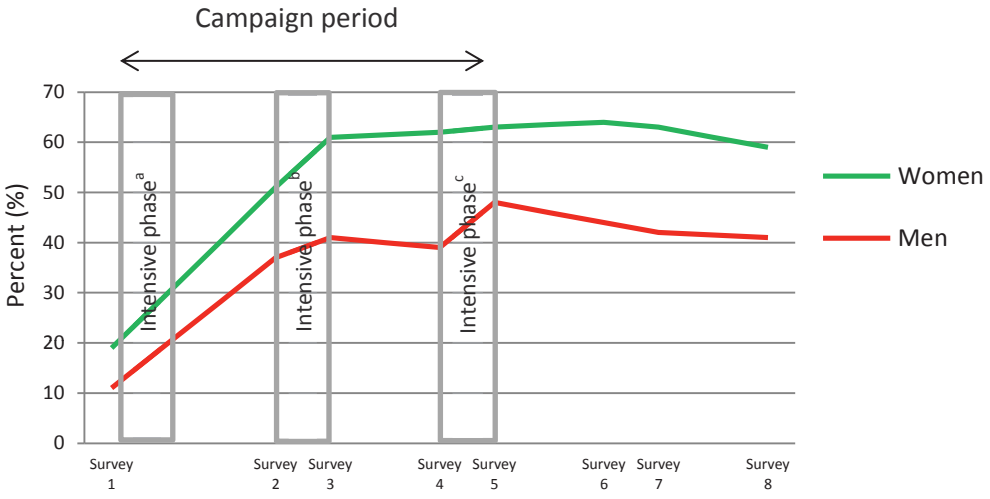

Figure 10. Respondents (%) recalling having heard about the AKUT test, by sex. [a]Directed to the general public. [b]Directed primarily to workplaces and sport clubs. [c]Directed primarily to men and younger individuals.

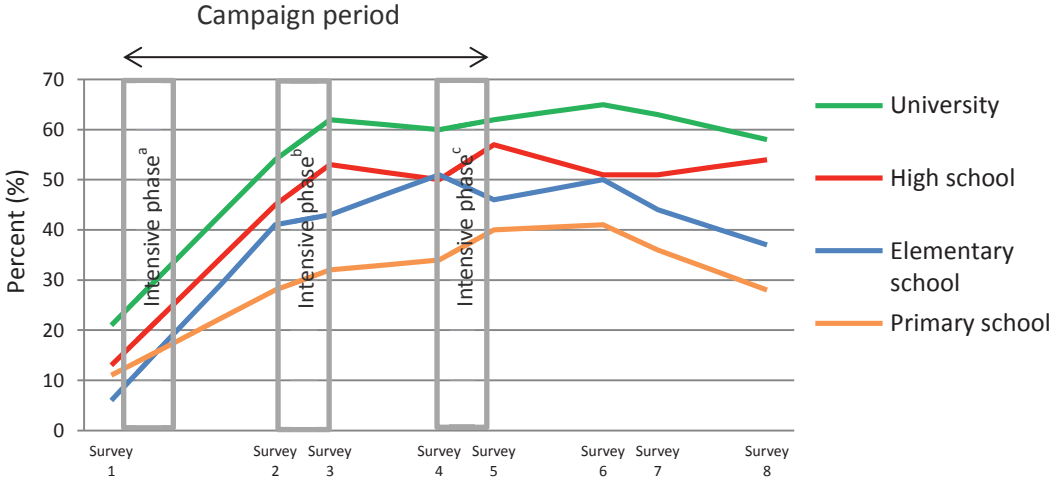

Figure 11. Respondents (%) recalling having heard about the AKUT test, by level of education. [a]Directed to the general public. [b]Directed primarily to workplaces and sport clubs. [c]Directed primarily to men and younger individuals.

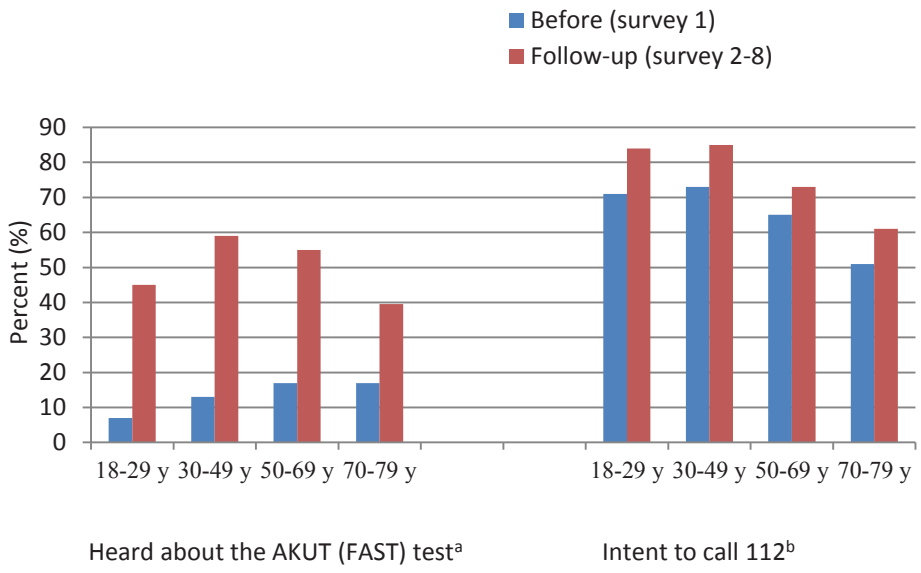

Figure 12. Improvement in different age groups on knowledge of the AKUT test ant intent to call 112 (%). [a]Significant interaction between age and improvement, $p < 0.0001$, [b]Significant interaction between age and improvement, $p = 0.0028$.

Study III

A flow chart illustrating the study population is given in Figure 13. The demographics were similar over time (Table 4).

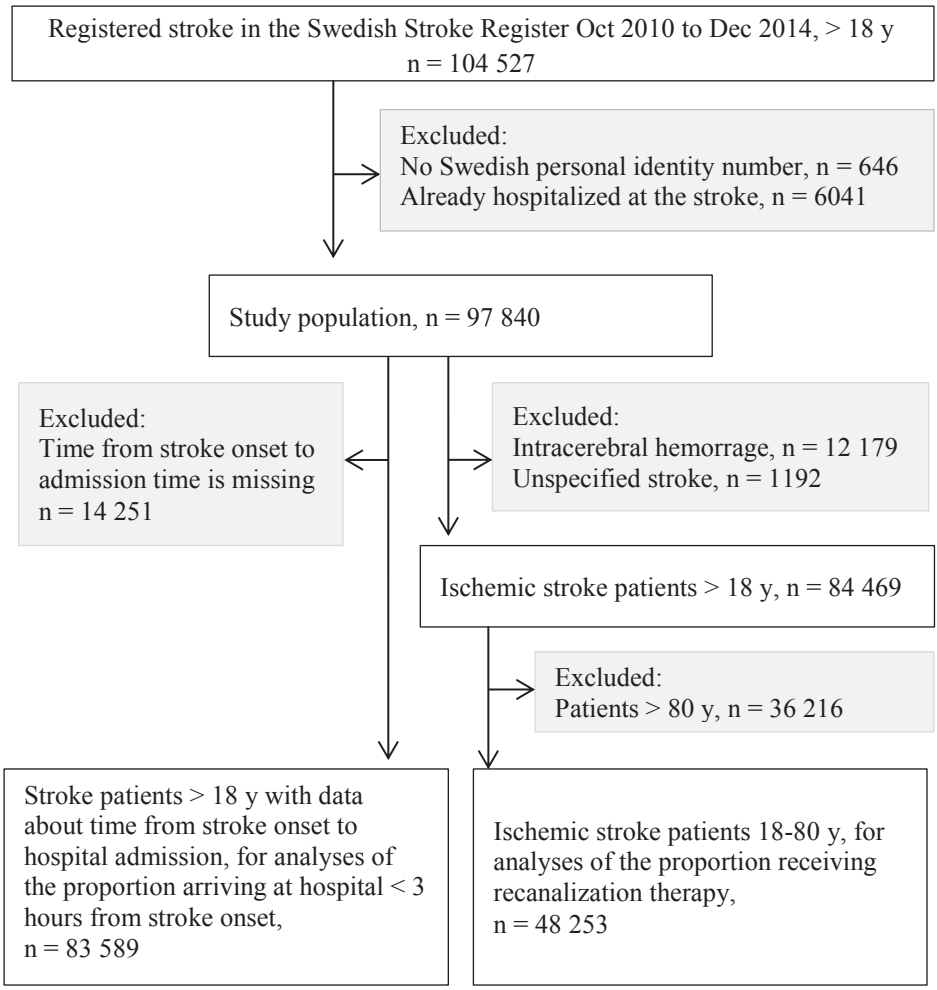

Figure 13. Flow chart of the study population.

Variable	12 months pre campaign, n = 23 702	27 months during the campaign, n = 52 054	12 months post campaign, n = 22 084
Sex			
Male, n (%)	12144 (51)	27997 (52)	11577 (52)
Female, n (%)	11558 (49)	25057 (48)	10507 (48)
Age group			
18-54 y, n (%)	1343 (5.7)	3122 (6.0)	1336 (6.0)
55-64 y, n (%)	2484 (10)	5649 (11)	2273 (10)
65-74 y, n (%)	5395 (23)	12065 (23)	5365 (24)
75-84 y, n (%)	7675 (32)	16406 (32)	6816 (31)
85+ y, n (%)	6805 (29)	14812 (28)	6294 (29)
Education			
Primary school, n (%)	11149 (45)	23420 (45)	9460 (43)
Secondary school, n (%)	10038 (42)	22644 (44)	10006 (45)
University ≥3 years, n (%)	1953 (8.2)	4895 (9.4)	2199 (10)
Country of birth			
Sweden and other Nordic, n (%)	22066 (93)	48414 (93)	20446 (93)
Other European, n (%)	705 (3.0)	1560 (3.0)	671 (3.0)
Other, n (%)	923 (3.9)	2070 (4.0)	962 (4.4)
Community size			
> 200 000, n (%)	7233 (31)	15187 (30)	6359 (29)
40 000-200 000, n (%)	8813 (38)	19908 (39)	8454 (39)
< 40 000, n (%)	7267 (31)	16050 (31)	6816 (32)
Living conditions			
Living alone[a], n (%)	11891 (50)	25910 (50)	10885 (50)
Previous stroke, n (%)	5871 (25)	12595 (24)	5121 (23)
ADL-independent[a], n (%)	19558 (84)	42995 (84)	18214 (84)
Living in an institution[a], n (%)	2475 (10)	5148 (9.9)	2230 (10)
Level of consciousness			
Alert, n (%)	19347 (82)	42683 (83)	18339 (84)
Drowsy, n (%)	2877 (12)	6161 (12)	2483 (11)
Unconscious, n (%)	1261 (5.4)	2540 (4.9)	1031 (4.7)
Stroke subtype			
Ischemic, n (%)	20434 (86)	44966 (86)	19069 (86)
Haemorrhagic, n (%)	2898 (12)	6461 (12)	2820 (13)
Unspecified, n (%)	370 (1.6)	627 (1.2)	195 (0.9)

Table 4. Demographics of the study population. Discrepancies between the proportion and the number for individual variables are due to missing data. [a]Before stroke onset.

Arrival at hospital within three hours from stroke onset

Time from stroke onset to hospital admission could be determined in 80.4% of the patients the year before the campaign started, in 86.4% during and in 88.7% the year after the campaign. The proportions of patients arriving at hospital within three hours from stroke onset at each quarter during the study period are given in Figure 14. A significant positive trend was seen only during the campaign (p = 0.033).

The year before the campaign started, 36.3% of the stroke patients arrived at hospital within three hours from stroke onset. This proportion increased to 37.2% in the last twelve months of the campaign and 37.4% the year after the campaign (before vs during the campaign; p = 0.364, before vs after the campaign; p = 0.029, and during vs after the campaign; p = 0.094). The crude odds ratio of arriving at hospital within three hours for the last twelve months of the campaign compared to the twelve months before the campaign was 1.04 (0.97 to 1.08). However, after adjustment for predefined possible confounders, there was a significant association between arrival at hospital within three hours and the last twelve months of the campaign (OR 1.05; 95% CI 1.00-1.09).

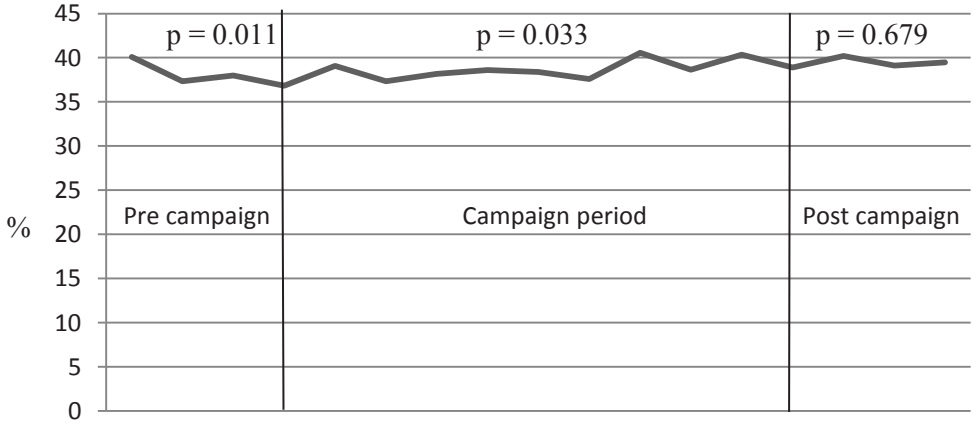

Figure 14. Proportion (%) arriving at hospital within three hours from stroke onset. p-values from Cochran-Armitage test for trend**.**

Recanalization therapy

Data about recanalization therapy could be determined in > 99% of all patients with ischemic stroke aged 18-79 years. The proportions of patients receiving recanalization therapy at each quarter during the study period are given in Figure 15. A significant positive trend was seen only during the campaign ($p < 0.001$). The year following the campaign there was no further improvement, but the proportion receiving recanalization therapy remained stable.

The year before the campaign start, 10.3% received recanalization therapy. This proportion increased to 13.3% in the last twelve months of the campaign and 13.2% the year after the campaign (before vs during the campaign; $p < 0.001$, before vs after the campaign; $p < 0.001$, and during vs after the campaign; $p = 0.190$). The crude odds ratio of receiving recanalization therapy for the last twelve months of the campaign compared to the twelve months immediately before the campaign was 1.33 (95% CI 1.23-1.45). This association remained significant after adjustment (OR 1.34; 95% CI 1.24-1.46).

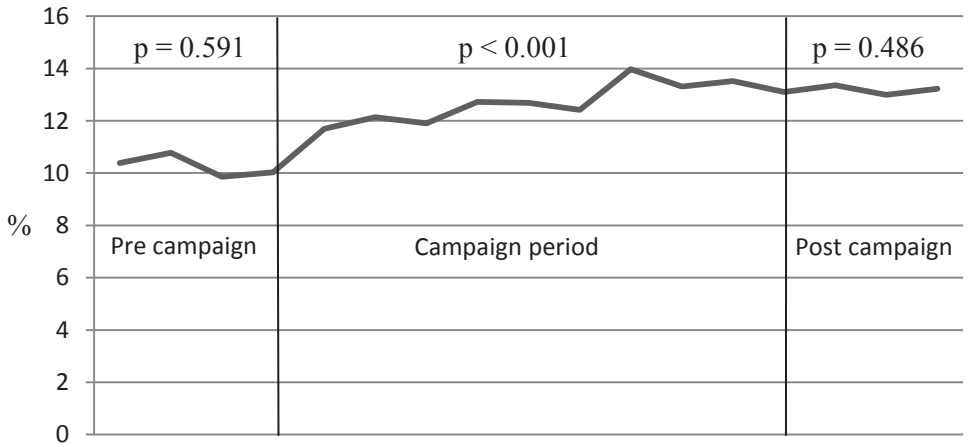

Figure 15. Proportion (%) receiving recanalization therapy (patients 18-80 y with ischemic stroke). p-values from Cochran-Armitage test for trend.

Study IV

Of the 466 patients identified as eligible for the study, 418 (90%) gave their informed consent to participate in the study (Figure 16).
After a study duration of five years, only 75 out of the estimated 150 patients were operated on within 48 hours. The number of patients with CEA within 48 hours was hence substantially lower than expected, and also decreased during the course of the study. Given the slow and descending inclusion rates in the very urgent CEA group, we found it unrealistic to include 150 patients with very urgent CEA in a foreseeable future. The study was therefore prematurely terminated on December 31, 2015. Baseline demographics, risk factors and technical data of the study population are presented in table 5.

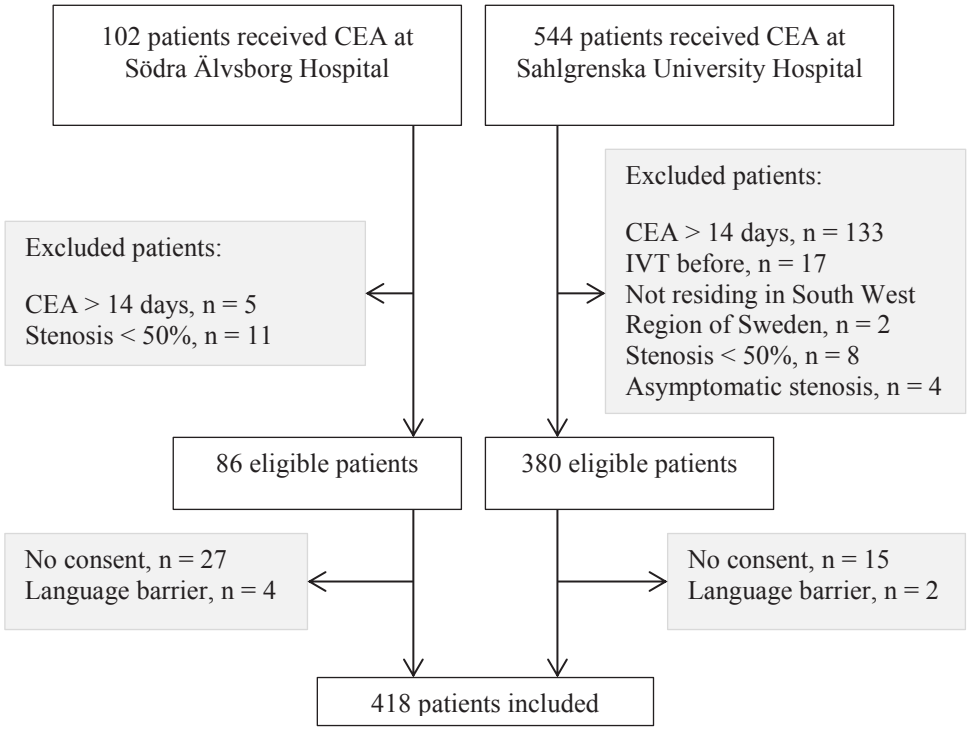

Figure 16. A flow diagram of all patients treated by carotid endarterectomy (CEA) at the two participating centers. IVT = Intravenous thrombolysis.

Delay to carotid endarterectomy from onset of most recent ischemic event	< 48 hours (n = 75)	48 hours - 14 days (n = 343)
Age, mean (SD)	73.1 (8.5)	73.7 (8.5)
Female, n (%)	20 (27)	106 (31)
Functional outcome before surgery (mRS[a] ≤ 2)	70 (93)	324 (94)
Degree of stenosis (NASCET[b])		
50-69%, n (%)	16 (21)	101 (29)
70-99%, n (%)	59 (79)	242 (71)
Degree of contralateral stenosis (NASCET[b])		
< 50%, n (%)	66 (88)	251 (73)
50-69%, n (%)	4 (5)	33 (10)
70-99%, n(%)	5 (7)	42 (12)
Occlusion, n(%)	0 (0)	17 (5)
Qualifying event[c]		
Amaurosis fugax/Retinal occlusion, n (%)	18 (24)	82 (24)
TIA, n (%)	28 (37)	106 (31)
Crescendo TIA, n (%)	14 (19)	17 (5)
Minor stroke, n (%)	15 (20)	137 (40)
Major stroke, n (%)	0 (0)	1 (0,3)
New ischemic event after the event that brought the patient to hospital, n (%)	37 (49)	37 (11)
New stroke after the event that brought the patient to hospital, n (%)	7 (9)	6 (2)
Risk factors		
Diabetes mellitus, n (%)	15 (20)	76 (22)
Hypertension, n (%)	58 (77)	264 (77)
Current smoking, n (%)	16 (21)	80 (23)
Coronary artery disease, heart failure, n (%)	27 (36)	117 (34)
Pulmonary disease, n (%)[d]	5 (7)	31 (9)
Surgery during out of office hours, n (%)	37 (49)	152 (44)
Days between the qualifying event and CEA, mean (SD)	1.3 (0.69)	6.7 (2.9)

Table 5. Baseline demographics, risk factors and technical data of the study population. [a]The modified Rankin Scale. [b]The North American Symptomatic Carotid Endarterectomy Trial. [c]Most recent ischemic event proceeding surgery. [d]Symptomatic chronic obstructive pulmonary disease.

Primary and secondary outcomes

Patients undergoing CEA within 48 hours from the most recent event had a significantly higher risk of the combined primary endpoint of mortality and/or any stroke compared with the group treated 48 hours to 14 days after an ischemic event; 8.0% versus 2.9% (OR 2.90; 95% CI 1.02–8.23), see Table 6. The characteristics of the 16 patients who suffered a complication are shown in Table 7. Multivariable logistic regression analyses showed that CEA performed within 48 hours (OR 3.07; 95% CI 1.04–9.09), CEA performed out of office hours (OR 3.65; 95% CI 1.14–11.67), and use of shunt (OR 4.02; 95% CI 1.36–11.93) were all independently associated with an increased risk of reaching the primary endpoint.

Primary and secondary outcomes	< 48 h n = 75	48 h–14 d n = 343	p-value[a]	OR very urgent CEA[b] (95% CI)[c]
Stroke and/or death, n (%)	6 (8.0)	10 (2.9)	0.049	2.90 (1.02-8.23)
Stroke, n (%)	6 (8.0)	9 (2.6)	0.035	3.23 (1.11-9.36)
Ipsilateral stroke, n (%)	6 (8.0)	7 (2.0)	0.016	4.17 (1.36-12.80)
Ipsilateral ischemic stroke, n (%)	6 (8.0)	5 (1.5)	0.006	5.88 (1.75-19.81)

Table 6. Primary and secondary outcomes. [a]Statistical analysis by Fisher´s exact test. [b]Carotid endarterectomy. [c]Bivariable odds ratio (OR) and 95% confidence intervals (CIs) were calculated using logistic regression analysis.

Post hoc analysis

Post hoc analysis showed that the combined mortality and/or stroke rate for patients operated within 48 hours from the event that brought the patient to hospital was 10.9% (five out of 46 patients). In contrast, the combined mortality and/or stroke rate for patients operated on within 48 hours from the most recent event, but more than 48 hours from the event that brought the patient to hospital was only 3.4% (one out of 29 patients).

Sex, age	Type of event[a]	Preop mRS	Time to CEA[b]	Endpoint, timing and type of endpoint	mRS at day 30
F, 75	Stroke	1	9 d	Day 3[e], ipsilateral hemorrhagic stroke, death	6
F, 67	Afx	1	2 d	Day 0-2[c], Ipsilateral ischemic stroke	2
M, 62	TIA	0	4 d	Day 0[d], Ipsilateral ischemic stroke	1
M, 72	Stroke	1	3 d	Day 0[d], Ipsilateral ischemic stroke	3
M, 70	Stroke	1	3 d	Day 0-2[c], Ipsilateral ischemic stroke	0
M, 78	TIA	1	5 d	Day 1, Contralateral ischemic stroke	0
M, 79	Stroke	2	6 d	Day 28, Contralateral ischemic stroke	1
M, 69	TIA	0	9 d	Day 2[e], Ipsilateral hemorrhagic stroke	5
M, 82	Stroke	1	6 d	Day 28, Death (in sepsis)	6
F, 75	RI	1	6 d	Day 0[d], Ipsilateral ischemic stroke	0
M, 83	TIA	0	<48 h	Intraoperative, Ipsilateral ischemic stroke	1
M, 74	Stroke	3	<48 h	Intraoperative, Ipsilateral ischemic stroke	3
M, 72	Afx	0	<48 h	Day 1, Ipsilateral ischemic stroke	5
F, 81	cTIA	2	<48 h	Day 0-2[c], Ipsilateral ischemic stroke	2
F, 79	TIA	0	<48 h	Intraoperative, Ipsilateral ischemic stroke	4
M, 74	Stroke	1	<48 h	Intraoperative, Ipsilateral ischemic stroke	4

Table 7. Characteristics of the patients who suffered a primary endpoint. F = Female; M = Male; Afx = Amaurosis fugax; cTIA = Crescendo TIA; RI = Retinal infarction; mRS = The modified Rankin Scale; Preop = preoperative; CEA = Carotid endarterectomy. [a]Most recent ischemic event preceding surgery. [b]Time to surgery was calculated as time from the most recent ischemic event preceding surgery. [c]Observed by neurologist at day two. [d]Symptom onset a few hours postoperatively. [e]No evidence for hyperperfusion syndrome (no hypertension and no headache).

Discussion

General discussion

The aim of this thesis was to generate knowledge that can improve timely acute treatment and secondary prevention in patients with acute cerebrovascular events. As “time is brain” both with respect to acute treatment and secondary prevention, such knowledge may, by a reduction of both the acute brain injury and the devastating effects of a recurrent stroke, increase the number of people surviving an acute stroke with no or only minor disability.

With respect to acute treatment, the focus was on reducing patients´ delay to activation of emergency services. In the first study, we confirmed a rather low public awareness of stroke in Sweden, justifying the efforts of the educational Swedish National Stroke Campaign launched by the Swedish Authorities. Next, we compared data from telephone surveys and national registers before, during and after the Swedish National Stroke Campaign and found significant improvements in stroke awareness in the general population as well as an increased proportion of patients receiving recanalization therapy, coinciding with the time for the campaign. A small but significant improvement regarding the proportion arriving to the hospital within three hours was also observed.

With respect to timely secondary prevention, the focus was on very urgent carotid surgery in patients with symptomatic carotid stenosis, investigating the hypothesis that very urgent surgery is not associated with an increased procedural risk compared to surgery performed later. However, opposite to our hypothesis, we found that very urgent surgery (within 48 hours of an ipsilateral cerebrovascular ischemic event) was associated with an increased risk of primary endpoint death and/or any stroke within 30 days of the surgical procedure compared with surgery performed 48 hours to 14 days after the event.

Public stroke awareness in Sweden

The inability to recognize stroke symptoms and to act optimally has been suggested to constitute the single most important factor explaining patients´ delay to activating emergency services, and thus also an important barrier for use of recanalization therapy in eligible cases (45). In this first study of stroke awareness, conducted in the general Swedish population, we confirm a rather low public awareness of stroke. Only about one out of ten could report three or more stroke symptoms and about two thirds indicated intent to call 112 when witnessing or experiencing a potential stroke. This is in line with findings from similar studies conducted in other countries (2). Men and those with lower level of education had poorer knowledge of stroke symptoms and risk factors. Among men there are also a significantly lower proportion that indicated intent to call 112 for stroke symptoms. In contrast to other studies (49), increased age was not associated with lower knowledge of risk factors and stroke symptoms. However, with increasing age a lower proportion indicated intent to call 112 if experiencing or witnessing a potential stroke, suggesting that elderly may have a higher threshold for activating emergency services. Earlier studies show that minority ethnic groups have constantly been reported to have poor stroke knowledge (49, 108). Study I included only those able to speak Swedish, why it is unclear whether non-Swedish speaking individuals were reached by the campaign.

Did the Swedish National Stroke Campaign increase stroke knowledge and intent to call 112?

Study II showed improved public stroke awareness both with respect to stroke knowledge and intent to call 112 during the campaign. Of note, the rate of improvement was higher during the first, most intensive part of the campaign and remained stable or decreased after the campaign ended, indicating that the observed improvements was an effect of the campaign. Similar results have been reported previously. One review (56), including 22 studies of educational stroke campaigns, concluded that all studies but one proved partially effective with respect to stroke awareness.

The only negative study was a four year long national campaign in the Czech Republic (60), differing from the others with respect to lower intensity and a very small budget (< 5% of the budget for the Swedish National Stroke Campaign).

It is also of note that the changes that occurred during the campaign closely coincided with the execution of the campaign. For instance, the proportions that had heard about the AKUT test and that could recall some or all keywords markedly increased during the first, most intensive, part of the campaign and the proportion that had heard about the AKUT test remained stable thereafter. In contrast, the proportion that could recall some or all keywords decreased during the latter part of the campaign, a period during which the campaign did not describe the AKUT keywords in detail.

Moreover, to reach men better, the latter part of the Swedish National Stroke Campaign linked advertising to sport programs, a context considered more appealing to men. After this specific part that targeted men, the rate of improvement regarding the knowledge about the AKUT test increased among men. These efforts may explain why this campaign reached men better than what was reported from another study (57) that found that women's knowledge improved more during a campaign. In our study, there was no sex difference in knowledge improvement. Also, the relative improvement during the course of the campaign for both stroke knowledge and intent to call 112 was independent by educational level despite differences in level of knowledge pre campaign.

In line with previous reports (62, 109), we found that elderly improved less during the course of the campaign, both with respect to intent to call 112 and knowledge about the AKUT test.

The observed changes during and after the Swedish National Stroke Campaign differs compared to other studies with respect to post campaign changes (61). Compared with previous stroke campaigns, there was a relatively modest decline in public knowledge post campaign, which may be explained by the additional web-based follow-up campaign. However, it is reasonable to assume that more intensive follow-up campaigns are needed to sustain the gains.

In conclusion, results from study II supports that the Swedish National Stroke Campaign increased public knowledge of the AKUT test and the need to call 112 when experiencing or witnessing a stroke, but intent to call 112 declined post-intervention. The greatest improvements occurred during the most intensive part of the campaign. Taken together, these results indicate a close relation between campaign intensity and effects and that repeated public information are essential to sustain the gains. Better strategies to reach older people are needed as this group improved less, especially as the elderly represent an important target for educational campaigns, both because this group has lower intent to call 112, but also because they are more likely to experience a stroke themselves or to witness it as a bystander.

Did the Swedish National Stroke Campaign influence patient behavior (patient delay) consequences of behavior (recanalization therapy)?

Study III demonstrated a significant increased improvement in both the proportion receiving recanalization therapy and the proportion arriving at hospital within three hours from stroke onset. For both outcomes, a significant improvement was seen only during the campaign period, indicating an association with the campaign. According to a systematic review (55), positive intervention effects were reported in the majority of studies. However, the success of a health awareness campaign is dependent on a multitude of factors, including the adequacy of funding, frequency of advertising, and use of appropriate media (110). A stepped-wedge cluster randomized controlled trial (111), with four clusters, did not demonstrate any effect on pre-hospital delay. However, the length of the intervention in this study was rather short and ranged between three months in the fourth and twelve months in the first cluster. A population-based study (112) investigating the effect of the FAST campaign in the UK showed marked improvement with respect to early presentation after major stroke (defined as NIHSS > 3) following the campaign. The FAST campaign was repeated regularly during several years. The length and/or repetition of the intervention might thus be critical (113).

Data on long-term effects from stroke campaigns are scarce. The majority of studies examining emergency department presentations for stroke symptoms, pre-hospital delay and/or recanalization rates in stroke patients report that the effect decline post intervention (63-66). However, a decline post intervention was not observed in our study as the proportions receiving recanalization therapy remained stable the year following the campaign. A possible explanation is an effect from the smaller additional follow-up campaign (conducted the year following the main campaign).

The Swedish National Stroke Campaign was directed towards the general population. It was therefore unexpected that there was a greater effect on the proportion receiving recanalization therapy than the proportion arriving at hospital within three hours. This could partly be explained by the shortcomings associated with the outcome variable "arrived within three hours from stroke onset". These shortcomings include imprecise estimations of the time for stroke onset reported by patients, bystanders or caregivers, and a possible influence of information bias as the proportion with data available on time from stroke onset to hospital arrival changed during the study period. This may limit the precision of the variable as an outcome measure, which is further discussed in the methodological considerations below.

In addition, during the campaign the hospitals also focused on improving the quality of in-hospital stroke care and reducing treatment delays. Door-to-needle times markedly improved during the campaign, after several preceding years with only modest improvements (114), which is in line with results reported elsewhere (115). Thus, according to the quality register Riksstroke, the years before the campaign started, median door-to-needle time was almost 70 minutes, and during the campaign the median time decreased substantially to 48 minutes in 2013. After the end of the campaign, the door-to-needle times have continued to improved but at a less rapid pace (45 minutes in 2014, 43 minutes in 2015 and 2016 respectively and 39 minutes in 2017), indicating that the observed substantial improvement during the campaign period possibly also was related to the efforts linked to the Swedish National Stroke Campaign.

A similar spillover effect was seen in the pre-hospital HASTA study (116) conducted in 2008 in Stockholm, Sweden. Patients with symptoms of stroke within six hours were randomized from the emergency medical services to either get an ambulance transport immediately (intervention group) or within 30 minutes (control group and, at that time, standard care). Interestingly, the observed in-hospital time reduction was even greater than the pre-hospital time reduction, despite the fact that the HASTA trial intervention was pre-hospital.

In conclusion, results from study III show that the Swedish National Stroke Campaign was associated with a sustained improvement regarding the proportion receiving recanalization therapy, and with a small but significant improvement regarding the proportion arriving at hospital within three hours.

Procedural risk of CEA stratified for delay

The Carotid Alarm Study (study IV) showed, contrary to our hypothesis, a significant increase in procedural risk if surgery was performed within the first 48 hours from an ischemic event compared to after 48 hours and up to 14 days after an ischemic event.

During the time period when the Carotid Alarm Study was ongoing, a number of other studies that investigated urgent carotid surgery were published. The reported risk associated with very early carotid intervention in these trials was divergent and partially conflicting (96-105, 117-121). The divergent findings may partly be explained by differences with respect to study design (i.e. prospective cohort studies versus retrospective and registry-based studies), inclusion/exclusion criteria and the exact definition of the qualifying event. However, there is no clear pattern on how such differences between studies influence the results and the overall heterogeneity across studies also limits the possibilities for meta-analysis.

The risk of underestimating complications associated with very urgent surgery is higher if a retrospective design is used. Register-studies can either be prospective or retrospective depending on when the register is filled in.

Except for the Carotid Alarm Study, we found a few other prospective studies (96, 100) (registry-based studies not included). Capoccia et al (96), included 48 patients with crescendo-TIA or stroke in evolution and reported a mortality and/or stroke rate of only 2.1% (i.e. one patient). Tsivgoulis et al (100) included 20 patients operated with CEA within 48 hours from stroke onset, of which two (10.0%) patients suffered a stroke.

In 2015, a meta-analysis (106) showed that early CEA within the first two days from a TIA was relatively safe, with a periprocedural stroke risk of 2.7%. However, when a stroke was the qualifying event, the periprocedural risk was substantially higher (8%). Therefore, studies including a higher proportion of TIA patients may underestimate the risk, compared with studies including a higher proportion of stroke patients.

The definition of qualifying event differs between studies. In some studies the qualifying event was defined as the referring event (i.e. the event that brought the patient to the doctor), and in other studies the most recent event was defined as the qualifying event. Studies reporting time from the most recent event tend to show a lower procedural risk than studies with the referral event as qualifying event. Hypothetically, patients with new symptoms after seeking medical care (a common situation if the qualifying event was defined as the most recent) may have had properly instituted medical therapy for a longer time period, which may stabilize the atherosclerotic plaque and hence decrease the risk of complications. In the Carotid Alarm Study, where the combined mortality and/or stroke rate was 8.0% in patients undergoing CEA within 48 hours, the qualifying event was defined as the most recent event prior to surgery. However, in post hoc analysis, the combined mortality and/or stroke rate for patients operated on within 48 hours from the event that brought the patient to hospital was 10.9%. In contrast, the combined mortality and/or stroke rate for patients operated on within 48 hours from the most recent event, but more than 48 hours from the event that brought the patient to hospital was only 3.4% (one out of 29 patients). Thus, the differences in definitions of qualifying event may affect the risk of a periprocedural stroke. A summary of studies analyzing risk of very urgent CEA is presented in Table 8.

In addition, with a very urgent treatment approach, both more treatment decisions and CEAs will be performed out-of office hours, with potentially reduced staffing levels, staffing seniority and supportive services at hospitals with worsening patient outcomes.

Given the diverse results in the literature regarding perioperative risk in very urgent carotid CEA, the Carotid Alarm Study adds further evidence in favor of a more careful approach with expedited CEA, within the first two days after an ischemic event. This is in line with the results presented in a very recent published systematic review and meta-analysis (122) that concluded that very urgent carotid intervention within the first two days was associated with increased risk of stroke within 30 days of treatment compared with urgent carotid intervention, 6.6% versus 3.2% (OR 2.19, 95% CI 1.46-3.2). However, this meta-analysis did not investigate patients with TIA or stroke separately, and therefore it is unclear if there is differences in complication frequencies depending on the type of qualifying event.

Thus, the optimal timing of CEA intervention following symptom onset still remains unclear. The anticipated theoretical benefit of very early surgery for symptomatic carotid artery stenosis has to be carefully balanced with the possibly increased risks associated with early intervention.

	Country	Design	Time for CEA from referral event/most recent event	Patients, n	Stroke/ Death, n (%)
Avgerinos 2017 (117)	U.S.	Register-study, multi	referral event	96	7 (7.3)
Barbetta 2014 (97)	Italy	Retrospective, single	referral event	45	2 (4.4)
Capoccia 2012 (96)	Italy	Prospective, single	referral event	48	1 (2.1)
Chisci 2015 (98)	Italy	Retrospective, single	referral event	30	3 (10.0)
Loftus 2016 (118)	U.K.	Register-study, national	referral event	780	29 (3.7)
Strömberg 2012 (101)	Sweden	Register-study, national	referral event	148	17 (11.4)
Tsantilas 2017 (123)	Germany	Retrospective, single	referral event	60	2 (3.3)
Tsivgoulis 2014 (100)	Greece	Prospective, multi	referral event	20	2 (10.0)
Nordanstig 2017	Sweden	Prospective, two centers	most recent event (referral event)[a]	75 (46)[a]	6 (8.0) (5 (10.9))[a]
Ferrero 2014 (102)	Italy	Retrospective, single	most recent event	176	7 (4.0)
Gajin 2014 (103)	Serbia	Retrospective, single	most recent event	58	0 (0.0)
Rantner 2015 (104)	Austria	Retrospective, single	most recent event	206	9 (4.4)
Sharpe 2013 (105)	U.S.	Retrospective, single	most recent event	41	1 (2.4)
Tsantilas 2016 (121)	Germany	Register-study, national	most recent event	5198	156 (3.0)

Table 8. Comparing procedural risk within 48 hours or two days from referral event (the event that brought the patient to hospital) or the most recent event. Relevant studies, published from 2012-2017, with $\geq$ 20 patients that performed CEA within 48 hours/two days are included. [a]Post-hoc analysis.

Methodological considerations and limitations

The results of research must always be interpreted in light of the weaknesses and strengths of the methods used. When conducting a clinical study there are a number of methodological considerations. In the planning phase, these include choosing an appropriate study design, recruitment of participants, and which specific methods to use. What to choose depends on the research question, but also on what is feasible.

Studies can be descriptive or analytical (effect research) studies. In an analytical study, the effect of something is studied, either as an analytical observational study ("the natural experiment") or as an analytical experimental study. Approaches such as cohort and case-control studies are examples of analytical observational studies. Examples of analytical experimental studies are RCTs and community intervention trials (Figure 17). An analytical study can be a controlled study (with a control group) or an uncontrolled study (without a control group). An experimental controlled study can further be a randomized controlled study or a non-randomized controlled study, in which people are allocated to different interventions using methods that are not random.

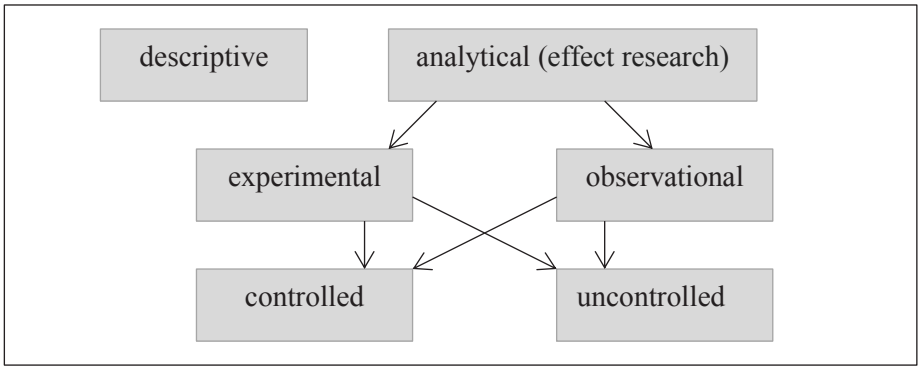

Figure 17: Type of studies.

During the course of a study and during the analytical phase unexpected issues may occur that may influence the results of the study (124-129). Methodological considerations with respect to study design and specific method, as well as the most important issues that occurred during the course of the studies and during data analysis, are presented below.

Study design

Descriptive study (study I):
To investigate public stroke awareness in Sweden, there are no other options than to use a descriptive study design. The methodological considerations are rather the choice of specific methods (telephone, face-to-face, postal or web-based questionnaires), see below.

Uncontrolled before, during and after study (study II and study III) - analytical studies:
The campaign was launched, designed and conducted by SALAR. The decision was to make it national and that the whole population should benefit. The possibility to perform a study using a regional control group in Sweden was not possible. Thus, the choice was to conduct an uncontrolled study comparing data from before, during and after the campaign. The main limitation however, with such studies is that causation cannot be proven.

An attractive design would have been a cluster randomized controlled trial. In cluster randomized trials clusters of people or communities, rather than individuals, are randomized to intervention and controlled groups. Avoiding withholding the intervention from a proportion of the participants, a so called stepped-wedge cluster randomized controlled trial (SW-RCT) (130) can be an alternative. This study design is a relatively new type of cluster randomized design. There is a period of baseline data collections, in which no clusters are exposed to the intervention. Subsequently, at periodic time points (“steps”), one cluster is randomized to cross from control to intervention, whereas the remaining clusters remain in the control condition. The study continues until all clusters have crossed to the intervention arm, and there is usually a period at the end of the study in which all cluster are

exposed to the intervention. However, even though this design can offer a whole population to be exposed to the campaign, the latest cluster included should be exposed for a shorter time period, and as the time exposed to a campaign seems to be essential, there may be some ethical considerations using this design.

In conclusion, as we could not influence the design of the campaign, neither a cluster randomized controlled study, nor a SW-RCT were feasible alternatives. Therefore, we found uncontrolled before, during and after studies to be the best alternative available.

A prospective controlled observational study (study IV):

The optimal study design for comparing acute CEA with subacute surgery is a randomized controlled trial (RCT). However, such a study will have to incorporate a large number of patients which is only possible as a multi-national multi-center randomized trial. Moreover, in the view of the documented high risk of recurrent events and as no studies at that time (before the start of study IV) showed an increased risk of perioperative complications with very early CEA (90), a study randomizing patients to delayed surgery might have caused difficulties in recruiting patients. Patients might have been reluctant to participate and investigators could have perceived an ethical dilemma to allocate patients to delayed surgery.

From our point of view and with the limited resources available, a RCT was not feasible and we found a prospective controlled study to be the best alternative. Such a study would give information about the procedural risk, and if not elevated it would strongly support very urgent surgery. However, if only a small proportion of patients are operated on very urgently there is a risk of aggregation of patients with unstable symptoms in the group undergoing surgery within 48 hours, which is a potential source of bias in such studies. To counteract this in the Carotid Alarm Study, we introduced a fast track for patients seeking within 24 hours from an ischemic event. Besides speeding up the process, the purpose of the fast track was to reduce the risk of selection bias in the group undergoing surgery within 48 hours. Our intent was to offer urgent surgery within 48 hours to all patients seeking within 24 hours from their last ischemic event. However, the use of a fast

track in a prospective study may facilitate urgent surgery in stable patients while unstable patients with higher risk for complications may be delayed due to additional time-consuming evaluations. Therefore, we believe that a possible selection bias in this study would, if anything, rather lead to an underestimation of the risk of complications associated with urgent surgery.

Specific methods

Telephone interviews (study I-II):

The aims of these studies were to evaluate the respondent´s knowledge in the area of stroke. It is important that the respondents are unprepared for the questions, which is the case when using telephone interviews. Contacting respondents by post or by the web would give an opportunity to search for the right answers before leaving a response. Therefore, postal or web-based surveys are not good alternatives for the evaluation of such knowledge. However, respondents have been shown to give more positive and socially desirable responses in telephone interviews compared to postal surveys (131). Therefore, reporting bias due to socially undesirable behaviors such as smoking and physical inactivity are likely to be underestimated in our studies. Besides the method of contacting respondents (telephone, face-to-face, postal or web-based questionnaires), the design of the questionnaire influences the answers from the respondents, e.g. if open-ended or closed-ended questions are used.

A possible selection bias would be if persons registered (about 75-80% of the target population) in the telephone register differ from persons not registered. As we do not have information about this, we can only speculate if this may have had influenced our results.

Another limitation is the selection bias with respect to minority ethnic groups. The survey was confined to those answering the telephone being able to speak Swedish, excluding a number of potential respondents. Results therefore cannot be generalized to non-Swedish speaking groups, which is important to be aware of because minority ethnic groups have consistently been reported to have poor stroke knowledge (49, 108).

Register-based study (study III):

A major strength of register-based studies is the potentially large size of the study populations. However, when data on a large numbers of patients are collected, detailed information is more difficult to obtain. Most violations of validity in a national register based study are the risk of selection bias, confounding factors and information bias.

Selection biases are distortions resulting from the procedures used to select study subjects. However, the registers used in study III have a high coverage during the study period, minimizing the selection bias. Confounding factors are associated with both the exposure and the outcome and they affect the true association between exposure and outcome. For instance, many aspects might affect onset to admission time, for example, the priority of stroke at the SOS-Alarm. Even if there has not been a change in priority for stroke patients in the instructions used by SOS-Alarm, they may also have been influenced by the campaign. If so, the effect of decreased onset to admission time may not reflect decreased patient´s delay but the early care of stroke patients. Information bias refers to measurement errors in the information needed to estimate an association. This could be caused by, either that important information is not registered in the register (predictable when planning the study) or missing data (unpredictable when planning the study). Examples of missing data in study III are described below.

Non-blinded evaluation of outcome (study IV):
The neurologists that examined the patients 30 days after CEA were not blinded with respect to treatment group, rendering a risk for observer bias. This bias could have been prevented by using independent clinicians who were not involved in the trial to assess patients. However, blinded outcome assessment was not practically feasible, as local physicians made the assessments and as patients were not blinded.

However, with the use of objective outcomes (mortality and stroke), non-blinded assessment was less likely to bias the results. Moreover, when there were difficulties to determine if a complication had occurred or not (one case), a senior external assessor reviewed the case after the medical record was censored from dates (that could reveal if CEA was performed within 48 hours or not).

Unexpected issues during the course of the studies

Misclassification in study II:
The question regarding knowledge about symptoms of stroke was an open-ended question. Difficulty with understanding or slurred speech, trouble walking/dizziness/loss of balance, unilateral numbness, unilateral weakness, headache and vision problems were classified as correct answers.
However, the proportion of respondents registered as correctly answering "unilateral weakness" when asked for stroke symptoms showed unreasonably large variations between the different surveys. This indicates that the interpretation of the answers by the interviewers differed over time and the professional telephone interviewing company admitted that the instructions to the interviewers seemed to have been too unclear. Thus, there is room for different interpretations and potential classification bias.

Therefore, we concluded that the results for this item were unreliable and we decided not to use any of the subqueries of this question in study II as an instrument to evaluate the effect of the campaign. Instead, the analyses were restricted to knowledge about the AKUT test and intent to call 112. This illustrates the importance of performing a face-to-face validation and/or a pilot study to identify unforeseen problems.

Slow inclusion rates in study IV:
During recruitment, the number of patients with CEA within 48 hours was substantially lower than expected, and also decreased during the course of the study. During the study period, we continuously investigated reasons for delay and took actions for speeding up the inclusion rate. However, given the slow and descending inclusion rates in the urgent CEA group, we found it unrealistic to include 150 patients with urgent CEA in a foreseeable future. Despite the fact that as many as 72% of the participants were admitted to the hospital within 24 hours from an ischemic event, only 11% underwent surgery within 48 hours. The main reasons for postponed surgery were organizational/logistical and not medical. As a consequence of the premature termination, this study is limited by a small sample.

Methodological considerations with respect to results and data analysis

Non-response bias (study II):
The response rate was somewhat low, and declined gradually from 62% to 36%, primarily because of an increased proportion of people not available despite multiple callbacks. According to the professional telephone interviewing company, this phenomenon was not unique to our study and may relate to an increased use of caller ID display on phones. Non-response bias (one reason for selection bias) can become an issue when there are distinct differences between the people who participate in the survey and the people who do not participate.

This error's impact on results cannot easily be quantified as we do not have much data on the non-respondents. However, the demographics remained stable during all surveys. This may indicate that there were no distinct differences between the people who participated and those who did not (independent loss of participants).

Missing data (study III):

Our initial aim was to analyze time from stroke onset to contact with emergency services and the proportion calling 112. To this end we used the unique personal identity number to link data from SOS-Alarm and Riksstroke. However, due to a large proportion of cases lacking personal identity numbers in the SOS-Alarm register, there was a high rate of non-linkage between the two registers. Therefore, the analyses were restricted to arrival at hospital within three hours and proportion of ischemic strokes receiving recanalization treatment.

Furthermore, the proportion of patients with missing data on stroke onset time decreased during the study period. If the improved coverage was biased towards those with a more delayed hospital arrival, this could influence the results and lead to a reduced sensitivity to detect an increase in the proportion arriving at hospital within three hours.

Less sensitive endpoint (study III):

The outcome proportion of patients arriving at hospital within three hours from stroke onset appears to be a less sensitive endpoint, as illustrated by the substantial over-representation of reported stroke onset at half- or full hours. It thus seems that it is common for patients, bystanders or caregivers to estimate stroke onset time without knowing the exact time. This may limit the precision of the variable as an outcome measure.

Ethical considerations

There are a number of ethical considerations to take into account when planning a study. The scientific benefits must always be carefully weighed against the possible negative effects for the participants.

Ethical issues related to telephone interviews (study I and II), especially on sensitive topics, are that they can be perceived as a violation of the personal integrity. In the questionnaire used in study I and II, the participants were asked about their own risk factors which can be perceived as sensitive issues.

Register data research (study III) involves processing of personal data, which may be considered as an integrity violation. All stroke patients admitted to hospitals in Sweden are informed that they are registered in the national stroke register (Riksstroke), aiming to improve stroke care. Patients are informed that they have the right to non-participation as well as withdrawal from the register, and that data may be used for research purposes. However, as formal written informed consent is not obtained, there is an inherent risk that some patients are not fully informed.

In the Carotid Alarm Study (study IV) a fast track for patients with recent symptoms was introduced, which may have caused delayed management of patients not included in the fast track. However, also in routine every day care, patients with recent symptoms have the highest priority as they have the highest risk for new events.

In the Carotid Alarm Study, ethical considerations may also include that patients may not feel empowered to refuse participation, as they are dependent on the doctor and research nurse for their ongoing care. It can also take some time for the patient to thoroughly consider whether they want to participate in research, and the focus of the consultation may be inadequately shifted away from the patient to the research. This ethical dilemma is however less apparent in observational than in interventional studies, as participation does not affect the given treatment.

Conclusion to given aims

- We confirmed a rather low public awareness of stroke in Sweden, poorer among men and those with a low level of education. With increased age, a lower proportion indicated intent to call 112 if witnessing or experiencing a potential stroke.

- The Swedish National Stroke Campaign substantially increased population knowledge about the AKUT test and intent to call 112 when experiencing or observing stroke symptoms. Relative improvement for both intent to call 112 and knowledge about the AKUT test was independent of sex and education level, but dependent on age as older individuals improved less.

- The Swedish National Stroke Campaign was associated with a sustained increase in the proportion receiving recanalization therapy and with a small, but statistically significant, improvement in the proportion arriving at hospital within three hours.

- Patients with symptomatic carotid stenosis undergoing CEA within 48 hours had a higher risk of death and/or any stroke within 30 days of the surgical procedure compared with those operated on later.

Future perspectives

The inability to recognize stroke symptoms and call 112 is a central factor explaining patients delay in seeking urgent care for stroke. In order to reduce this delay, there are no other obvious ways to reach success than embarking on education efforts directed towards the general population. Stroke educational campaigns have a potential to increase stroke knowledge, reduce patients delay and increase the use of recanalization therapy.

Consequently, the main important question is not *if* educational programs are effective or not, but *how* to design the most effective educational program. Future studies should therefore focus on finding the most effective methods to reach the entire population, including all relevant subpopulations within the target audience. Cost effectiveness analysis on this topic is also of paramount important to guide healthcare decision makers to allocate limited resources.

One important challenge for future campaigns is how to optimize targeting of the elderly. Older individuals are an important target as they are more likely to both suffer and witness a stroke. In addition, older age is both independently associated with a longer time from stroke onset to admission at hospital (132) and with a significantly lower knowledge improvement during the Swedish National Stroke Campaign.

One way forward may be to cooperate with specialists in pedagogics and communication which might increase both penetration and retention of an educational effort within the entire population.

Repetition is perhaps the most intuitive principle of learning, which is why learning activities need to be repeated regularly. The effects of stroke educational campaigns decline post-intervention, both with respect to stroke knowledge and patient behavior, clarifying the importance of repetition. Therefore, future educational programs should be repeated regularly. The small additional follow-up campaign after the Swedish National Stroke Campaign may explain why the effects remained stable and did not decrease as we had expected.

With respect to urgent carotid surgery within the first two days after an ischemic event, it remains unclear whether the risk of complications outweighs the risk of recurrent stroke if carotid surgery is deferred. A clear answer may only be obtained by conducting a randomized controlled trial. However, such a study would require a large sample, which for several reasons may be very difficult to recruit, and therefore may not be feasible. In addition, there may be a high risk of crossovers, due to logistical issues, from the group with very early surgery intent to later surgery. In the absence of randomized trials, prospective data on large multicenter cohorts, investigating both the combined risk of recurrent stroke and procedural risk may be the second best but a more reasonable alternative. In such a study, patients should be included as soon as possible after an event. By urgently investigating all patients with TIA or minor stroke (with brain CT and CT angiography of the carotid arteries) and thereafter without delay recruit patients to a prospective study, selection bias would be reduced, thus enabling a study of the combined early risk of recurrent stroke as well as the periprocedural risk associated with carotid intervention.

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References

1. Mortality GBD, Causes of Death C. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet (London, England). 2016;388(10053):1459-544.
2. DALYs GBD, Collaborators H, Murray CJ, Barber RM, Foreman KJ, Abbasoglu Ozgoren A, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990-2013: quantifying the epidemiological transition. Lancet (London, England). 2015;386(10009):2145-91.
3. Feigin VL, Krishnamurthi RV, Parmar P, Norrving B, Mensah GA, Bennett DA, et al. Update on the Global Burden of Ischemic and Hemorrhagic Stroke in 1990-2013: The GBD 2013 Study. Neuroepidemiology. 2015;45(3):161-76.
4. Årsrapport-Riksstroke. 2016(http://www.riksstroke.org/wp-content/uploads/2017/07/Riksstroke%C3%85rsrapport2016_slutversion.pdf).
5. Socialstyrelsen. 2016(http://www.socialstyrelsen.se/statistik/statistikefteramne/stroke).
6. Stroke--1989. Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and other Cerebrovascular Disorders. Stroke; a journal of cerebral circulation. 1989;20(10):1407-31.
7. Krishnamurthi RV, Feigin VL, Forouzanfar MH, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet Glob Health. 2013;1(5):e259-81.
8. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol. 2009;8(4):355-69.
9. Appelros P, Jonsson F, Asberg S, Asplund K, Glader EL, Asberg KH, et al. Trends in stroke treatment and outcome between 1995 and 2010: observations from Riks-Stroke, the Swedish stroke register. Cerebrovascular diseases (Basel, Switzerland). 2014;37(1):22-9.
10. Ornello R, Degan D, Tiseo C, Di Carmine C, Perciballi L, Pistoia F, et al. Distribution and Temporal Trends From 1993 to 2015 of Ischemic Stroke Subtypes: A Systematic Review and Meta-Analysis. Stroke; a journal of cerebral circulation. 2018.
11. Xie X, Atkins E, Lv J, Bennett A, Neal B, Ninomiya T, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. Lancet (London, England). 2016;387(10017):435-43.
12. Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet (London, England). 2016;388(10059):2532-61.
13. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Annals of internal medicine. 2007;146(12):857-67.

14. Mons U, Muezzinler A, Gellert C, Schottker B, Abnet CC, Bobak M, et al. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium. BMJ (Clinical research ed). 2015;350:h1551.
15. O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet (London, England). 2016;388(10046):761-75.
16. Astrup J, Symon L, Branston NM, Lassen NA. Cortical evoked potential and extracellular K+ and H+ at critical levels of brain ischemia. Stroke; a journal of cerebral circulation. 1977;8(1):51-7.
17. Astrup J, Siesjo BK, Symon L. Thresholds in cerebral ischemia - the ischemic penumbra. Stroke; a journal of cerebral circulation. 1981;12(6):723-5.
18. Saver JL. Time is brain--quantified. Stroke; a journal of cerebral circulation. 2006;37(1):263-6.
19. Bang OY, Goyal M, Liebeskind DS. Collateral Circulation in Ischemic Stroke: Assessment Tools and Therapeutic Strategies. Stroke; a journal of cerebral circulation. 2015;46(11):3302-9.
20. Moustafa RR, Baron JC. Imaging the penumbra in acute stroke. Current atherosclerosis reports. 2006;8(4):281-9.
21. Liebeskind DS, Alexandrov AV. Advanced multimodal CT/MRI approaches to hyperacute stroke diagnosis, treatment, and monitoring. Ann N Y Acad Sci. 2012;1268:1-7.
22. Kidwell CS, Wintermark M, De Silva DA, Schaewe TJ, Jahan R, Starkman S, et al. Multiparametric MRI and CT models of infarct core and favorable penumbral imaging patterns in acute ischemic stroke. Stroke; a journal of cerebral circulation. 2013;44(1):73-9.
23. Vilela P, Rowley HA. Brain ischemia: CT and MRI techniques in acute ischemic stroke. European journal of radiology. 2017;96:162-72.
24. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). Jama. 1995;274(13):1017-25.
25. National Institute of Neurological D, Stroke rt PASSG. Tissue plasminogen activator for acute ischemic stroke. The New England journal of medicine. 1995;333(24):1581-7.
26. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet (London, England). 2014;384(9958):1929-35.
27. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet (London, England). 2016;387(10029):1723-31.
28. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. The New England journal of medicine. 2015;372(1):11-20.

29. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. The New England journal of medicine. 2015;372(11):1019-30.
30. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. The New England journal of medicine. 2015;372(24):2285-95.
31. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. The New England journal of medicine. 2015;372(11):1009-18.
32. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. The New England journal of medicine. 2015;372(24):2296-306.
33. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. The New England journal of medicine. 2018;378(1):11-21.
34. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. The New England journal of medicine. 2018;378(8):708-18.
35. Evans JW, Graham BR, Pordeli P, Al-Ajlan FS, Willinsky R, Montanera WJ, et al. Time for a Time Window Extension: Insights from Late Presenters in the ESCAPE Trial. AJNR American journal of neuroradiology. 2018;39(1):102-6.
36. Stroke Unit Trialists C. Organised inpatient (stroke unit) care for stroke. The Cochrane database of systematic reviews. 2013(9):CD000197.
37. Socialstyrelsen. Nationella riktlinjer för strokesjukvård. . 2018(https://roi.socialstyrelsen.se/riktlinjer/nationella-riktlinjer-for-vard-vid-stroke/3).
38. Coull AJ, Lovett JK, Rothwell PM, Oxford Vascular S. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. BMJ (Clinical research ed). 2004;328(7435):326.
39. Lovett JK, Coull AJ, Rothwell PM. Early risk of recurrence by subtype of ischemic stroke in population-based incidence studies. Neurology. 2004;62(4):569-73.
40. Esenwa C, Gutierrez J. Secondary stroke prevention: challenges and solutions. Vascular health and risk management. 2015;11:437-50.
41. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke; a journal of cerebral circulation. 2014;45(7):2160-236.
42. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ, Carotid Endarterectomy Trialists C. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. Lancet (London, England). 2004;363(9413):915-24.
43. Rothwell PM, Giles MF, Chandratheva A, Marquardt L, Geraghty O, Redgrave JN, et al. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. Lancet (London, England). 2007;370(9596):1432-42.

44. Evenson KR, Rosamond WD, Morris DL. Prehospital and in-hospital delays in acute stroke care. Neuroepidemiology. 2001;20(2):65-76.
45. Kwan J, Hand P, Sandercock P. A systematic review of barriers to delivery of thrombolysis for acute stroke. Age Ageing. 2004;33(2):116-21.
46. Jorgensen HS, Nakayama H, Reith J, Raaschou HO, Olsen TS. Factors delaying hospital admission in acute stroke: the Copenhagen Stroke Study. Neurology. 1996;47(2):383-7.
47. Clark JM, Renier SA. A community stroke study: factors influencing stroke awareness and hospital arrival time. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association. 2001;10(6):274-8.
48. Evenson KR, Foraker RE, Morris DL, Rosamond WD. A comprehensive review of prehospital and in-hospital delay times in acute stroke care. International journal of stroke : official journal of the International Stroke Society. 2009;4(3):187-99.
49. Jones SP, Jenkinson AJ, Leathley MJ, Watkins CL. Stroke knowledge and awareness: an integrative review of the evidence. Age Ageing. 2010;39(1):11-22.
50. Ramirez-Moreno JM, Alonso-Gonzalez R, Peral-Pacheco D, Millan-Nunez MV, Aguirre-Sanchez JJ. Knowledge of stroke a study from a sex perspective. BMC Res Notes. 2015;8:604.
51. Ramirez-Moreno JM, Alonso-Gonzalez R, Peral Pacheco D, Millan-Nunez MV, Roa-Montero A, Constantino-Silva AB, et al. Effect of socioeconomic level on knowledge of stroke in the general population: A social inequality gradient. Neurologia (Barcelona, Spain). 2016;31(1):24-32.
52. Reeves MJ, Rafferty AP, Aranha AA, Theisen V. Changes in knowledge of stroke risk factors and warning signs among Michigan adults. Cerebrovascular diseases (Basel, Switzerland). 2008;25(5):385-91.
53. Ferris A, Robertson RM, Fabunmi R, Mosca L, American Heart A, American Stroke A. American Heart Association and American Stroke Association national survey of stroke risk awareness among women. Circulation. 2005;111(10):1321-6.
54. Mochari-Greenberger H, Towfighi A, Mosca L. National women's knowledge of stroke warning signs, overall and by race/ethnic group. Stroke; a journal of cerebral circulation. 2014;45(4):1180-2.
55. Mellon L, Doyle F, Rohde D, Williams D, Hickey A. Stroke warning campaigns: delivering better patient outcomes? A systematic review. Patient Relat Outcome Meas. 2015;6:61-73.
56. Rasura M, Baldereschi M, Di Carlo A, Di Lisi F, Patella R, Piccardi B, et al. Effectiveness of public stroke educational interventions: a review. Eur J Neurol. 2014;21(1):11-20.
57. Miyamatsu N, Kimura K, Okamura T, Iguchi Y, Nakayama H, Toyota A, et al. Effects of public education by television on knowledge of early stroke symptoms among a Japanese population aged 40 to 74 years: a controlled study. Stroke; a journal of cerebral circulation. 2012;43(2):545-9.
58. Marx JJ, Klawitter B, Faldum A, Eicke BM, Haertle B, Dieterich M, et al. Gender-specific differences in stroke knowledge, stroke risk perception and the effects of an educational multimedia campaign. Journal of neurology. 2010;257(3):367-74.
59. Muller-Nordhorn J, Wegscheider K, Nolte CH, Jungehulsing GJ, Rossnagel K, Reich A, et al. Population-based intervention to reduce prehospital delays in

patients with cerebrovascular events. Archives of internal medicine. 2009;169(16):1484-90.
60. Mikulik R, Goldemund D, Reif M, Brichta J, Neumann J, Jarkovsky J, et al. Calling 911 in response to stroke: no change following a four-year educational campaign. Cerebrovascular diseases (Basel, Switzerland). 2011;32(4):342-8.
61. Hodgson C, Lindsay P, Rubini F. Can mass media influence emergency department visits for stroke? Stroke; a journal of cerebral circulation. 2007;38(7):2115-22.
62. Silver FL, Rubini F, Black D, Hodgson CS. Advertising strategies to increase public knowledge of the warning signs of stroke. Stroke; a journal of cerebral circulation. 2003;34(8):1965-8.
63. Flynn D, Ford GA, Rodgers H, Price C, Steen N, Thomson RG. A time series evaluation of the FAST National Stroke Awareness Campaign in England. PloS one. 2014;9(8):e104289.
64. Mellon L, Hickey A, Doyle F, Dolan E, Williams D. Can a media campaign change health service use in a population with stroke symptoms? Examination of the first Irish stroke awareness campaign. Emerg Med J. 2014;31(7):536-40.
65. Nishijima H, Ueno T, Kon T, Haga R, Funamizu Y, Arai A, et al. Effects of educational television commercial on pre-hospital delay in patients with ischemic stroke wore off after the end of the campaign. J Neurol Sci. 2017;381:117-8.
66. Advani R, Naess H, Kurz M. Mass Media Intervention in Western Norway Aimed at Improving Public Recognition of Stroke, Emergency Response, and Acute Treatment. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association. 2016;25(6):1467-72.
67. Bonifati DM, Lorenzi A, Ermani M, Refatti F, Gremes E, Boninsegna C, et al. Carotid stenosis as predictor of stroke after transient ischemic attacks. J Neurol Sci. 2011;303(1-2):85-9.
68. Ois A, Cuadrado-Godia E, Rodriguez-Campello A, Jimenez-Conde J, Roquer J. High risk of early neurological recurrence in symptomatic carotid stenosis. Stroke; a journal of cerebral circulation. 2009;40(8):2727-31.
69. Johansson EP, Arnerlov C, Wester P. Risk of recurrent stroke before carotid endarterectomy: the ANSYSCAP study. International journal of stroke : official journal of the International Stroke Society. 2013;8(4):220-7.
70. Tsantilas P, Kuhnl A, Kallmayer M, Knappich C, Schmid S, Kuetchou A, et al. Stroke risk in the early period after carotid related symptoms: a systematic review. The Journal of cardiovascular surgery. 2015;56(6):845-52.
71. Hansson GK, Robertson AK, Soderberg-Naucler C. Inflammation and atherosclerosis. Annu Rev Pathol. 2006;1:297-329.
72. Kirshner HS. Differentiating ischemic stroke subtypes: risk factors and secondary prevention. J Neurol Sci. 2009;279(1-2):1-8.
73. Battistella V, Elkind M. Intracranial atherosclerotic disease. Eur J Neurol. 2014;21(7):956-62.
74. Flaherty ML, Kissela B, Khoury JC, Alwell K, Moomaw CJ, Woo D, et al. Carotid artery stenosis as a cause of stroke. Neuroepidemiology. 2013;40(1):36-41.
75. DeBakey ME. Successful carotid endarterectomy for cerebrovascular insufficiency. Nineteen-year follow-up. Jama. 1975;233(10):1083-5.

76. Dyken ML, Pokras R. The performance of endarterectomy for disease of the extracranial arteries of the head. Stroke; a journal of cerebral circulation. 1984;15(6):948-50.
77. Easton JD. History of carotid endarterectomy then and now: personal perspective. Stroke; a journal of cerebral circulation. 2014;45(6):e101-3.
78. Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. The New England journal of medicine. 1998;339(20):1415-25.
79. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet (London, England). 1998;351(9113):1379-87.
80. North American Symptomatic Carotid Endarterectomy Trial C, Barnett HJM, Taylor DW, Haynes RB, Sackett DL, Peerless SJ, et al. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. The New England journal of medicine. 1991;325(7):445-53.
81. Rothwell PM, Eliasziw M, Gutnikov SA, Fox AJ, Taylor DW, Mayberg MR, et al. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. Lancet (London, England). 2003;361(9352):107-16.
82. Rothwell PM, Gibson RJ, Slattery J, Warlow CP. Prognostic value and reproducibility of measurements of carotid stenosis. A comparison of three methods on 1001 angiograms. European Carotid Surgery Trialists' Collaborative Group. Stroke; a journal of cerebral circulation. 1994;25(12):2440-4.
83. Wardlaw JM, Chappell FM, Best JJ, Wartolowska K, Berry E, Research NHS, et al. Non-invasive imaging compared with intra-arterial angiography in the diagnosis of symptomatic carotid stenosis: a meta-analysis. Lancet (London, England). 2006;367(9521):1503-12.
84. Hedayati N, Humphries MD, Zhou W. Gender and outcomes of carotid artery interventions. Vascular and endovascular surgery. 2014;48(2):99-105.
85. Jim J, Dillavou ED, Upchurch GR, Jr., Osborne NH, Kenwood CT, Siami FS, et al. Gender-specific 30-day outcomes after carotid endarterectomy and carotid artery stenting in the Society for Vascular Surgery Vascular Registry. Journal of vascular surgery. 2014;59(3):742-8.
86. Shahidi S, Owen-Falkenberg A, Gottschalksen B, Ellemann K. Risk of early recurrent stroke in symptomatic carotid stenosis after best medical therapy and before endarterectomy. International journal of stroke : official journal of the International Stroke Society. 2016;11(1):41-51.
87. Kragsterman B, Nordanstig A, Lindstrom D, Stromberg S, Thuresson M, Nordanstig J. Editor's Choice - Effect of More Expedited Carotid Intervention on Recurrent Ischaemic Event Rate: A National Audit. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2018;56(4):467-74.
88. Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons,

American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. Developed in collaboration with the American Academy of Neurology and Society of Cardiovascular Computed Tomography. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2013;81(1):E76-123.

89. Peeters W, Hellings WE, de Kleijn DP, de Vries JP, Moll FL, Vink A, et al. Carotid atherosclerotic plaques stabilize after stroke: insights into the natural process of atherosclerotic plaque stabilization. Arteriosclerosis, thrombosis, and vascular biology. 2009;29(1):128-33.

90. Health Technology assessment. 2009(https://alfresco.vgregion.se/alfresco/service/vgr/storage/node/content/workspace/SpacesStore/900f353c-2b86-4500-a1a5-396af88df0d1/2009_14 HTA-rapport Akutkirurgi vid TIA.pdf?a=false&guest=true).

91. Aleksic M, Rueger MA, Sobesky J, Heckenkamp J, Jacobs AH, Brunkwall J. Immediate CEA for symptomatic carotid disease preferably performed under local anaesthesia is safe. VASA Zeitschrift fur Gefasskrankheiten. 2007;36(3):185-90.

92. Brandl R, Brauer RB, Maurer PC. Urgent carotid endarterectomy for stroke in evolution. VASA Zeitschrift fur Gefasskrankheiten. 2001;30(2):115-21.

93. Dorigo W, Pulli R, Barbanti E, Azas L, Troisi N, Pratesi G, et al. Carotid endarterectomy in patients with acute neurological symptoms: a case-control study. Interactive cardiovascular and thoracic surgery. 2007;6(3):369-73.

94. Rantner B, Pavelka M, Posch L, Schmidauer C, Fraedrich G. Carotid endarterectomy after ischemic stroke--is there a justification for delayed surgery? European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2005;30(1):36-40.

95. Sbarigia E, Toni D, Speziale F, Acconcia MC, Fiorani P. Early carotid endarterectomy after ischemic stroke: the results of a prospective multicenter Italian study. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2006;32(3):229-35.

96. Capoccia L, Sbarigia E, Speziale F, Toni D, Biello A, Montelione N, et al. The need for emergency surgical treatment in carotid-related stroke in evolution and crescendo transient ischemic attack. Journal of vascular surgery. 2012;55(6):1611-7.

97. Barbetta I, Carmo M, Mercandalli G, Lattuada P, Mazzaccaro D, Settembrini AM, et al. Outcomes of urgent carotid endarterectomy for stable and unstable acute neurologic deficits. Journal of vascular surgery. 2014;59(2):440-6.

98. Chisci E, Pigozzi C, Troisi N, Tramacere L, Zaccara G, Cincotta M, et al. "Thirty-day neurologic improvement associated with early versus delayed carotid endarterectomy in symptomatic patients". Annals of vascular surgery. 2015;29(3):435-42.

99. Mussa FF, Aaronson N, Lamparello PJ, Maldonado TS, Cayne NS, Adelman MA, et al. Outcome of carotid endarterectomy for acute neurological deficit. Vascular and endovascular surgery. 2009;43(4):364-9.

100. Tsivgoulis G, Krogias C, Georgiadis GS, Mikulik R, Safouris A, Meves SH, et al. Safety of early endarterectomy in patients with symptomatic carotid artery stenosis: an international multicenter study. Eur J Neurol. 2014;21(10):1251-7, e75-6.
101. Stromberg S, Gelin J, Osterberg T, Bergstrom GM, Karlstrom L, Osterberg K, et al. Very urgent carotid endarterectomy confers increased procedural risk. Stroke; a journal of cerebral circulation. 2012;43(5):1331-5.
102. Ferrero E, Ferri M, Viazzo A, Labate C, Berardi G, Pecchio A, et al. A retrospective study on early carotid endarterectomy within 48 hours after transient ischemic attack and stroke in evolution. Annals of vascular surgery. 2014;28(1):227-38.
103. Gajin P, Radak D, Tanaskovic S, Babic S, Nenezic D. Urgent carotid endarterectomy in patients with acute neurological ischemic events within six hours after symptoms onset. Vascular. 2014;22(3):167-73.
104. Rantner B, Schmidauer C, Knoflach M, Fraedrich G. Very urgent carotid endarterectomy does not increase the procedural risk. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2015;49(2):129-36.
105. Sharpe R, Sayers RD, London NJ, Bown MJ, McCarthy MJ, Nasim A, et al. Procedural risk following carotid endarterectomy in the hyperacute period after onset of symptoms. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2013;46(5):519-24.
106. De Rango P, Brown MM, Chaturvedi S, Howard VJ, Jovin T, Mazya MV, et al. Summary of Evidence on Early Carotid Intervention for Recently Symptomatic Stenosis Based on Meta-Analysis of Current Risks. Stroke; a journal of cerebral circulation. 2015;46(12):3423-36.
107. Riksstroke Årsrapport 2011. 2011(http://www.riksstroke.org/wp-content/uploads/2014/05/Riks-Strokes_report_2011-English.pdf).
108. Gardois P, Booth A, Goyder E, Ryan T. Health promotion interventions for increasing stroke awareness in ethnic minorities: a systematic review of the literature. BMC Public Health. 2014;14:409.
109. Lecouturier J, Rodgers H, Murtagh MJ, White M, Ford GA, Thomson RG. Systematic review of mass media interventions designed to improve public recognition of stroke symptoms, emergency response and early treatment. BMC Public Health. 2010;10:784.
110. Steckler A, Allegrante JP, Altman D, Brown R, Burdine JN, Goodman RM, et al. Health education intervention strategies: recommendations for future research. Health Educ Q. 1995;22(3):307-28.
111. Denti L, Caminiti C, Scoditti U, Zini A, Malferrari G, Zedde ML, et al. Impact on Prehospital Delay of a Stroke Preparedness Campaign: A SW-RCT (Stepped-Wedge Cluster Randomized Controlled Trial). Stroke; a journal of cerebral circulation. 2017;48(12):3316-22.
112. Wolters FJ, Paul NL, Li L, Rothwell PM, Oxford Vascular S. Sustained impact of UK FAST-test public education on response to stroke: a population-based time-series study. International journal of stroke : official journal of the International Stroke Society. 2015;10(7):1108-14.
113. Merzel C, D'Afflitti J. Reconsidering community-based health promotion: promise, performance, and potential. Am J Public Health. 2003;93(4):557-74.

114. Riksstroke-Årsrapporter (http://www.riksstroke.org/sve/forskning-statistik-och-verksamhetsutveckling/rapporter/arsrapporter/).
115. Fonarow GC, Smith EE, Saver JL, Reeves MJ, Bhatt DL, Grau-Sepulveda MV, et al. Timeliness of tissue-type plasminogen activator therapy in acute ischemic stroke: patient characteristics, hospital factors, and outcomes associated with door-to-needle times within 60 minutes. Circulation. 2011;123(7):750-8.
116. Berglund A, Svensson L, Sjostrand C, von Arbin M, von Euler M, Wahlgren N, et al. Higher prehospital priority level of stroke improves thrombolysis frequency and time to stroke unit: the Hyper Acute STroke Alarm (HASTA) study. Stroke; a journal of cerebral circulation. 2012;43(10):2666-70.
117. Avgerinos ED, Farber A, Abou Ali AN, Rybin D, Doros G, Eslami MH, et al. Early carotid endarterectomy performed 2 to 5 days after the onset of neurologic symptoms leads to comparable results to carotid endarterectomy performed at later time points. Journal of vascular surgery. 2017;66(6):1719-26.
118. Loftus IM, Paraskevas KI, Johal A, Waton S, Heikkila K, Naylor AR, et al. Editor's Choice - Delays to Surgery and Procedural Risks Following Carotid Endarterectomy in the UK National Vascular Registry. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2016;52(4):438-43.
119. Stromberg S, Nordanstig A, Bentzel T, Osterberg K, Bergstrom GM. Risk of early recurrent stroke in symptomatic carotid stenosis. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2015;49(2):137-44.
120. Nordanstig A, Rosengren L, Stromberg S, Osterberg K, Karlsson L, Bergstrom G, et al. Editor's Choice - Very Urgent Carotid Endarterectomy is Associated with an Increased Procedural Risk: The Carotid Alarm Study. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2017;54(3):278-86.
121. Tsantilas P, Kuehnl A, Konig T, Breitkreuz T, Kallmayer M, Knappich C, et al. Short Time Interval Between Neurologic Event and Carotid Surgery Is Not Associated With an Increased Procedural Risk. Stroke; a journal of cerebral circulation. 2016;47(11):2783-90.
122. Milgrom D, Hajibandeh S, Hajibandeh S, Antoniou SA, Torella F, Antoniou GA. Systematic Review and Meta-Analysis of Very Urgent Carotid Intervention for Symptomatic Carotid Disease. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2018.
123. Tsantilas P, Kuhnl A, Kallmayer M, Pelisek J, Poppert H, Schmid S, et al. A short time interval between the neurologic index event and carotid endarterectomy is not a risk factor for carotid surgery. Journal of vascular surgery. 2017;65(1):12-20 e1.
124. Frieden TR. Evidence for Health Decision Making - Beyond Randomized, Controlled Trials. The New England journal of medicine. 2017;377(5):465-75.
125. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?". Lancet (London, England). 2005;365(9453):82-93.
126. Jones DS, Podolsky SH. The history and fate of the gold standard. Lancet (London, England). 2015;385(9977):1502-3.
127. Bothwell LE, Greene JA, Podolsky SH, Jones DS. Assessing the Gold Standard--Lessons from the History of RCTs. The New England journal of medicine. 2016;374(22):2175-81.

128. Kones R, Rumana U, Merino J. Exclusion of 'nonRCT evidence' in guidelines for chronic diseases - is it always appropriate? The Look AHEAD study. Curr Med Res Opin. 2014;30(10):2009-19.
129. Chavez-MacGregor M, Giordano SH. Randomized Clinical Trials and Observational Studies: Is There a Battle? J Clin Oncol. 2016;34(8):772-3.
130. Hemming K, Taljaard M. Sample size calculations for stepped wedge and cluster randomised trials: a unified approach. J Clin Epidemiol. 2016;69:137-46.
131. Bowling A. Mode of questionnaire administration can have serious effects on data quality. J Public Health (Oxf). 2005;27(3):281-91.
132. Eriksson M, Glader EL, Norrving B, Stegmayr B, Asplund K. Acute stroke alert activation, emergency service use, and reperfusion therapy in Sweden. Brain Behav. 2017;7(4):e00654.