

# LONG-TERM POST-STROKE OUTCOME

THE SAHLGRENSKA ACADEMY STUDY ON  
ISCHEMIC STROKE

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Cover illustration: Magnetic resonance tomography in 7-year follow-up after ischemic stroke, showing a brain infarction affecting the left cerebral middle artery.

*To Bengt, Adrian, Alvin, Didrik and Vendela*



# ABSTRACT

Independent studies report that stroke incidence in younger ages is increasing. Consequences after stroke include disability, cognitive dysfunction and the risk of stroke recurrence and coronary events. There are still many gaps of knowledge regarding post-stroke outcomes. Therefore the aim of the present thesis was to describe long-term prognosis in young and middle-aged ischemic stroke sufferers and to identify predictors of mortality and recurrent vascular events.

The studies were based on the Sahlgrenska Academy Study on Ischemic Stroke (SAHLSIS), with 1,090 consecutive adult patients and 600 controls, all younger than 70 years. All participants were very well characterized at baseline with respect to vascular risk factors, life-style and socioeconomic factors. Patients were classified according to etiologic subtype, i.e. large vessel disease (LVD), small vessel disease (SVD), cardioembolic stroke (CE), cryptogenic stroke, other determined stroke and undetermined stroke. Stroke severity was assessed. Two years after index stroke surviving patients were contacted for a structured telephone interview, with questions about recurrent vascular events and assessment of functional outcome. After 7 years patients participated in a follow-up visit to a study physician and a study nurse, and were tested with the Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS). Data on mortality and recurrent vascular were collected through national registers and medical records for both cases and controls.

First, we investigated 2-year outcomes in patients. We showed that stroke severity, the subtype of LVD, and hypertension were independent predictors of the composite outcome (death and/or recurrent vascular events). With regards to functional outcome, stroke severity was also an independent predictor of dependency.

Next, we investigated very long-term outcomes. After 12-year follow-up stroke incidence was 10 times higher in cases compared to controls, whereas the incidence of coronary events was only twofold higher in cases. Both diabetes and smoking were independent predictors of the composite outcome (recurrent vascular events), and diabetes also independently predicted both mortality and coronary events. Living alone was a strong and independent predictor of mortality, and also predicted stroke recurrence. There was an interaction between living alone and gender, with highest mortality among males living alone. Living alone also showed association to mortality in controls. An increased risk of coronary events was found among physically inactive patients. A personal history of stroke predicted the composite outcome and stroke recurrence, whereas a personal history of coronary heart disease showed association to all outcomes except stroke recurrence. Patients with the subtype of LVD and CE stroke had an increased mortality rate, and LVD also showed an increased incidence of the composite outcome. Stroke severity was associated with all outcomes except coronary events. We found the BNIS to be a promising screening instrument for cognitive dysfunction after ischemic stroke, and our results indicate that a large proportion of younger stroke patients may have cognitive dysfunction many years after stroke.

In conclusion, young and middle-aged ischemic stroke patients face a high and sustained risk of mortality and recurrent vascular events many years after stroke. In addition to classical vascular risk factors, stroke subtype and stroke severity influence outcome events. Moreover, emerging modifiable lifestyle factors such as living alone and physical activity have an impact on mortality and the rate of recurrent vascular events, and some of these effects vary by endpoint. Thus, further studies are needed to develop more patient-tailored secondary prevention measures in order to improve long-term outcomes after ischemic stroke.

**Keywords:** stroke, cohort studies, prognosis, predictor, ischemic stroke subtypes, functional outcome, mortality, myocardial infarction, social isolation, living alone, cognitive dysfunction

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# LIST OF ORIGINAL PAPERS

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# ABBREVIATIONS

BI	Barthel Index
BNIS	The Barrow Neurological Institute Screen for Higher Cerebral Functions
CE	Cardioembolic
CHD	Coronary heart disease
CI	Confidence interval
CT	Computer tomography
ECG	Electrocardiogram
HR	Hazard ratio
ICD	International Classification of Diseases
IHD	Ischemic heart disease
IQR	Interquartile range
LVD	Large vessel disease
MI	Myocardial infarction
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
OR	Odds ratio
PAD	Peripheral artery disease
SAHLSIS	Sahlgrenska Academy Study on Ischemic Stroke
SSS	Scandinavian Stroke Scale
SVD	Small vessel disease
TIA	Transient ischemic attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment
WHR	Waist-hip-ratio
WMD	White matter disease



## INTRODUCTION

Stroke is the second most common cause of mortality worldwide, only ischemic heart disease (IHD) claims more victims.[1] The global burden of disease study from 2010 states that the overall burden of stroke has increased the past 20 years; it is now ranked as the third most common cause of disability-adjusted life year compared to 5<sup>th</sup> place in 1990.[2] In Sweden about 30000 suffer a stroke every year and stroke is the third cause of death. Whereas IHD mortality has declined steeply in Western countries,[3] the decline in stroke mortality is more modest.[4] However, independent studies report that the incidence of stroke is increasing in younger ages and thus do not match the mortality decline, either globally or in Sweden[5-7] Mortality and disability in young and middle-aged stroke sufferers have great social and economic consequences both for society and for the individual, as this age group is in a demanding phase of life and has a long life expectancy.[8] Moreover, new vascular events in these individuals lead to increased disability. Therefore, identifying predictors of mortality and vascular events in this age group is important and may ultimately give us new opportunities to customize and individualize secondary prevention.

### **Stroke: definition, pathology and classification**

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.”[9] Symptoms lasting <24 hours are called transient ischemic attack (TIA). Stroke is classified as ischemic or hemorrhagic based on the underlying pathology. Neuroimaging with either computer tomography (CT) or magnetic resonance imaging (MRI) is required for an accurate classification.

In ischemic stroke, a blood vessel becomes partly or totally obstructed and this leads to lack of blood supply, causing focal cerebral ischemia and cell necrosis. In hemorrhagic stroke a blood vessel ruptures and leads to an intracranial bleeding. The blood compresses and distorts the cerebral tissue, causing cell necrosis. Hemorrhagic stroke can further be classified as intracerebral hemorrhage and subarachnoid hemorrhage, based on the site and origin of the bleeding. Worldwide, the incidence of ischemic stroke is twice as high as hemorrhagic stroke,[10, 11] but in high-income countries such as Sweden,

ischemic stroke is the predominant stroke type and constitutes >85%.[12] The present studies focus only on ischemic stroke.

### **Ischemic stroke subtypes**

Ischemic stroke is a heterogeneous disease and can be divided into etiologic subtypes, based on the underlying pathophysiological mechanism. An increasing body of evidence suggests that stroke subtype influences short-term prognosis after ischemic stroke. The impact on long-term prognosis is not fully elucidated, and is one of the focus subjects of this thesis. The most widely used classification system is the Trial of Org. 10172 in Acute Stroke Treatment (TOAST).[13] The subtypes consist of large vessel disease (LVD), small vessel disease (SVD), cardioembolic (CE) stroke, stroke of other determined etiology, undetermined stroke and cryptogenic stroke.

#### **Large vessel disease (LVD)**

About 15-20% of all strokes are caused by LVD, but the proportion varies by age, sex and ethnicity.[14] LVD is atherosclerotic disease in large and medium sized precerebral and cerebral arteries. The atherosclerotic plaques typically develop near branching points and places of confluence. In white populations the atherosclerotic plaques are more frequent in the extracranial arteries whereas intracranial atherosclerosis is more prevalent among the Asian, Hispanic and black populations. The reason for the different distribution is unknown.

Cerebral ischemia by atherosclerosis may be caused by distal artery to artery embolization from an atherosclerotic lesion (considered the most common mechanism) or by hemodynamic mechanisms.

#### **Small vessel disease (SVD)**

This subtype accounts for one quarter of all ischemic stroke. According to the lacunar hypothesis,[15] a lacunar infarction is the result of an occlusion of a single deep perforating end-artery arising from the circle of Willis or from the basilar artery.[16] The most common locations are the deep white matter, the internal capsule, the thalamus and the paramedian and lateral regions of the brainstem. The infarcts are usually small (0.2-15mm). The pathology is not clear but microatheroma, intimal thickening and hyalinization and wall fibrosis in the small penetrating vessels have been described.[17] The clinical manifestations of a lacunar syndrome include pure motor hemiparesis, pure

sensory stroke, sensorimotor stroke, ataxic hemiparesis and dysarthria-clumsy hand syndrome and atypical lacunar syndromes.[15]

However, in up to 20% of cases, a lacunar syndrome may also be caused by for example an embolic occlusion of cardiac or arterial origin or by vasculitis. Therefore, a thorough diagnostic work-up should be done, to exclude other causes than SVD.[18]

### Cardioembolic (CE) stroke

CE stroke is considered to cause approximately 25% of all ischemic strokes, but in elderly patients it is the most common subtype[13, 19] Embolism from the heart to the brain leads to a vessel occlusion and the most common underlying etiology is atrial fibrillation. Recent myocardial infarction (MI), mechanical prosthetic valve, dilated cardiomyopathy, mitral rheumatic stenosis, atrial myxoma, and endocarditis are also considered as high-risk sources of cardioembolism. Studies show that CE strokes are often severe, have a sudden onset of symptoms and have a high early recurrence rate.[20, 21] Another characteristic of CE stroke is the high proportion of hemorrhagic transformation compared with non CE strokes.[22]. In contrast to other stroke subtypes, anticoagulation with vitamin K antagonists is effective as preventive medication after most CE stroke. Recently, new direct oral anticoagulants have also received approval for stroke prevention in non-valvular atrial fibrillation.[23]

### Cryptogenic stroke

Cryptogenic stroke accounts for 25-30% of all ischemic strokes and is more prevalent among young stroke sufferers.[24] An ischemic stroke is classified as cryptogenic if the etiology cannot be identified despite an extensive work-up. In most studies, cryptogenic stroke has not been defined as a separate subtype, but included in the undetermined stroke category.[24-27]

It has been suggested that the proportion of cryptogenic stroke could be reduced by putting more effort on the diagnostic work-up.[28] Many studies in recent years have focused on revealing potential etiologies that may have escaped detection in the initial work-up, i.e. with prolonged ambulatory electrocardiogram (ECG) and insertable cardiac monitoring, atrial fibrillation was found in 9-16% of patients with cryptogenic stroke.[29, 30] However, whether there was a causal relation with the index stroke is unknown. Patent foramen ovale and atrial septum aneurysm have been reported to be more prevalent among cryptogenic stroke[31], but randomized studies have failed to show a benefit on recurrent stroke rate with device closure.[32, 33]

### Other determined stroke

In about 5% of all ischemic stroke cases the cause is of other determined etiology[34] and this proportion is higher the younger the population is (up to 16% in patients <50 years).[35] The most common cause in this category is arterial dissection. Other more rare causes include hematological disorders, vasculitis, complications of cardiovascular procedures, monogenic syndromes, and migraine stroke.

### Undetermined stroke

The cases where multiple etiologies are identified and where the work-up is incomplete are classified as undetermined. Consequently, the proportion for this category varies depending on how much effort is spent on diagnostic evaluation.[36]

## **Long-term prognosis after ischemic stroke**

Prognosis and predictors of outcome for young stroke patients versus all ages are different.[25] Similarly, it is probably not correct to assume that prognosis and prognostic baseline variables for either very young stroke patients or stroke patients in all ages are applicable for young and middle-aged stroke sufferers. Long-term follow-up studies after ischemic stroke either include all ages, most often with a mean age of 70 years or more, or younger ages, with patients being <50 years at stroke onset. While, the proportion of patients suffering an ischemic stroke before the age of 50 years in Sweden is quite low (<5%), the proportion under 70 years is about 37%.[7] Most of these individuals are still in working age and have many years left to live. This thesis is therefore focused on this important age group.

### Mortality

Studies after ischemic stroke report the 5-year mortality in the range of 6-58%.[37-48] The risk of mortality in studies including patients <55 years is 6-11% while the mortality in studies in all ages ranges from 41-58%. Thus, most of the variation can probably be explained by age, where the risk of death in studies on young stroke is low. Differences may to some extent also be explained by study design, i.e. including all patients or only patients surviving 30 days after index stroke and by reduced risk of mortality over time.[49] Table 1 summarizes previously published large studies on mortality after ischemic stroke with follow-up  $\geq 2$  years.



**Table 1.** Studies examining mortality rates and/or independent predictors of mortality  $\geq 2$  years after ischemic stroke, including  $>400$  patients (studies including cerebral hemorrhages or TIA excluded).

	Age	N	Mortality	Subtype	Associated riskfactors*
Rutten-Jacobs	<50	606	6% 5y	Yes	Age, CE stroke <sup>∞</sup>
Putala	<50	731	11% 5y	Yes	Age, DM, alcohol, malignancy, infection, HF, LVD
Aarnio	<50	970	6% 5y	Yes	Age, DM, HF, alcohol, malignancy, stroke severity, LVD, CE, SVD, UD stroke, rare cause subtype
Greisenegger	<55	671	8% 5y	No	Age, DM, alcohol, HF, PAD
Lv Yumei	64 <sup>Ω</sup>	710	11% 4y	No	Age, male gender, HT, CHD, depression, stroke severity**
Nam	65 <sup>Ω</sup>	3278	18% 3y	No	Age, length of stay, aspirin <sup>†</sup> , statin <sup>†</sup> , stroke severity, CE, LVD, undetermined stroke
Ntaios	≈70 <sup>Ω</sup>	2,730	≈41% 5y	Yes	Age, smoking, HF, aspirin <sup>†</sup> , AC <sup>†</sup> , ACE or ARB <sup>†</sup> , statin <sup>†</sup> , CE stroke severity
Kammersgaard	74 <sup>Ω</sup>	899	58% 5y	No	Age, DM, smoking, AF, previous stroke, stroke severity
Carter	70 <sup>Ω</sup>	545	57% 5y	No	Age, previous stroke/TIA, AF, PACI, POCI, TACI
Koton	71 <sup>Ω</sup>	1,079	31% 3y	No	Age, DM, HF, PAD, malignancy, history of dementia, low level of consciousness, temperature, glucos on admission, TACI
Melkas	71 <sup>Ω</sup>	486	50% 5y	No	Age, HF, smoking, SVD, stroke severity
Kolominsky Rabas	73 <sup>Ω</sup>	583	32% 2y	Yes	Age, CE <sup>∞</sup>
Petty	75 <sup>Ω</sup>	1,111	53% 5y	No	Age, AF, HF, CHD, recurrent stroke
Vernino	75 <sup>Ω</sup>	444	46% 5y	Yes, but not TOAST	Age, prior MI, angina, HF, AF, major medical complications within 10 days, aspirin, AC <sup>†</sup> , CE stroke, stroke severity
Petty	76 <sup>Ω</sup>	454	53% 5y	Yes, but not TOAST	Age, HF, LVD <sup>†</sup> , stroke severity
Giang	<55	17,149	7% 4y	NA	NA
Hartmann	70 <sup>Ω</sup>	980	41% 5y	NA	NA
Schmidt	74 <sup>Ω</sup>	53,545	46% 5y	NA	NA
Ronning	76 <sup>Ω</sup>	550	55% 5y	NA	NA

Y indicates year; CE, cardioembolic; DM, diabetes mellitus; HF, heart failure; PAD, peripheral artery disease; LVD, large vessel disease; AF atrial fibrillation; TIA, transient ischemic attack; PACI; partial anterior circulation infarction; POCI, posterior circulation infarction; TACI, total anterior circulation infarction; CHD, coronary heart disease; MI, myocardial infarction; AC, anticoagulantia; ACE, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; TOAST, Trial of Org. 10172 in Acute Stroke Treatment; NA, non applicable.

\*Independent associations. <sup>∞</sup>Adjusted for gender, but no other risk factors. <sup>Ω</sup>mean, <sup>†</sup>Protective.

\*\*Variables associated with lacunar infarction, n=474.

## Recurrent stroke

The reported stroke recurrence rate 5 years after stroke ranges from 9-32% [25, 27, 35, 48, 50-54]. The variation in recurrence rate may be explained by the aforementioned factors, [55] but moreover, some studies have excluded fatal recurrent stroke whereas others have included all stroke. Stroke recurrence is highest the first week, and also higher the first year after stroke compared to the subsequent years. [56] Table 2 shows previously published large studies reporting independent predictors of recurrent stroke and follow-up 2 years.

**Table 2.** Studies examining independent predictors of recurrent stroke  $\geq 2$  years after ischemic stroke, including >400 patients (studies including cerebral hemorrhages or TIA excluded).

	Age	N	Recurrent stroke rate	Subtypes	Associated riskfactors*
Pezzini	<45	1,867	11% 5y	Yes	History of migraine, family history of stroke, medication discontinuation (antiplatelets and antihypertensive), antiphospholipid antibodies
Rutten- Jacobs	<50	447	10% 5y	Yes	Atherothrombotic stroke, CE stroke, SVD compared to cryptogenic <sup>∞</sup>
Putaalaa	<50	807	9% 5y	Yes	Age, DM, previous TIA, LVD compared to SVD
Lv Yumei	64 <sup>Ω</sup>	710,	11% 4y	No	Male gender <sup>†</sup> , DM, mild depression**
Hier	≈69	1,273	14% 2y	Yes, but not TOAST	DM, HT, prior stroke, unknown cause of stroke <sup>†</sup>
Ntaios	70 <sup>Ω</sup>	2,730	≈20% 5y	Yes	Age, previous TIA, smoking <sup>†</sup> , statin usage <sup>†</sup>
Kolominsky Rabas	73 <sup>Ω</sup>	583	10% 2y	Yes	Age <sup>§</sup>
Petty	75 <sup>Ω</sup>	1,111	29% 5y	No	Age, DM
Petty	76 <sup>Ω</sup>	454	≈32% 5y	Yes, but not TOAST	DM

Y indicates year; CE, cardioembolic; SVD, small vessel disease; DM, diabetes mellitus; TIA, transient ischemic attack; LVD, large vessel disease; HT, hypertension; TOAST, Trial of Org. 10172 in Acute Stroke Treatment. \*Independent associations. <sup>∞</sup>TIA included. <sup>§</sup>Adjusted for gender, but no other risk factors. <sup>Ω</sup>Mean. <sup>†</sup>Protective. \*\*Variables associated with lacunar infarction, n=474.

### Coronary events

Age is of major importance for incident coronary event after ischemic stroke and studies including only young patients report coronary event rates ranging from 0.7-5%[25, 35, 53] after 5 years compared to 5-14%[27, 54, 57] in studies with patients of all ages. However, definitions of coronary events also differ within these studies, with some studies including revascularization procedures (coronary artery bypass and/or percutaneous interventions) and others that do not. Current evidence suggests that the risk of MI after an ischemic stroke is around 1.9% per year.[58] The risk seems to be somewhat higher the first year after stroke,[53, 54] but considerably lower than the risk of recurrent stroke even after many years of follow-up.[27, 35, 53]

### Functional outcome

Functional outcome after ischemic stroke may be assessed in various ways, one of the most common being the modified Rankin Scale (mRS).[59] The second most common disability scale (which assesses ability to care for oneself) is the Barthel index (BI).[60, 61] However, limitations of the BI include the focus on voluntary motor functions, which leads to an underestimation of disability among patients with for example aphasia and a “ceiling” effect in mild stroke patients.[60] Other disability scales, e.g. the Stroke Impact Scale, and the Functional Independence Measure, have been used to a lesser extent. Disadvantages of these include that they are time-consuming. However, the mRS has also been criticized because it is influenced by comorbidities and socioeconomic factors.[59]

Most long-term follow-up studies on functional outcome have included all stroke (i.e. both ischemic and hemorrhagic stroke), whereas functional outcome after ischemic stroke is more unexplored.[39] However, at long-term follow-up, 6-31% of ischemic stroke survivors were dependent.[62-66] These studies had variable follow-up time (3 to 9 years), but disability level was usually stable over time.[64]

### **Predictors of long-term mortality and recurrent stroke**

Long-term is defined as the more than 1-year follow-up in the following sections. Knowledge about baseline variables predicting long-term mortality and recurrent stroke after ischemic stroke is somewhat limited. Most old studies were conducted on overall stroke, and it is therefore difficult to draw any conclusions from these studies, as predictors of outcome after hemorrhagic

stroke are clearly not the same as after ischemic stroke.[67] There are also limitations with previous studies conducted on ischemic stroke: important predictors such as stroke subtype and severity have typically not been included and the number of patients have often been small, making multivariable analysis difficult.[51] Moreover, studies have seldom taken into account socioeconomic and life-style factors.

### Demographics

Increasing age is associated with long-term mortality after ischemic stroke in almost all studies whereas female gender was reported to be protective only in a few studies.[68, 69] A consistent finding is also the influence of increasing age on recurrent stroke rate. This applies both for studies in young stroke patients and studies in all ages. Mortality after stroke is higher in low-income countries than in high-income countries, but it remains unclear whether or not mortality differs by ethnicity after taking into account hospital characteristics, socioeconomic status and stroke severity.[70, 71]

### Classical risk factors

Treatment of hypertension is of major importance for reducing the stroke burden worldwide[72] and treatment of hypertension after stroke has top priority in the Swedish national guidelines for stroke care.[73] Against this background it is remarkable that only a few long-term follow-up studies after ischemic stroke have reported an independent association for baseline hypertension with mortality,[74] or with recurrent stroke.[75, 76]. Moreover, current data do not provide any support for an association in young stroke patients. The explanation is not clear but may be a result of effective secondary hypertensive treatment or the fact that the threshold for definition of hypertension among patients having suffered a stroke need to be lower.

Likewise, hyperlipidemia/hypercholesterolemia was associated with mortality after 10 years in a small study conducted more than 15 years ago.[76] Recent studies did not find any association, and this may be explained by revised recommendations with a higher proportion of patients receiving statins in recent years. Waist-hip-ratio, body mass index, and obesity have been included only in a few long-term studies and did not influence long-term mortality or recurrent stroke in these.[41, 74]

There is substantial evidence from many studies that diabetes mellitus is a major risk factor for long-term mortality, both in young stroke patients and in all ages.[38, 42, 68, 77, 78] A partial explanation may be a different risk factor and

etiologic profile among patients with diabetes.[79] Diabetes has also been shown to increase the risk of recurrent stroke.[25, 48, 74, 75]

### Socioeconomic and life-style factors

Smoking is a major risk factor for incident stroke,[80] but an association to increased mortality has only been shown in some long-term follow-up studies in all ages,[27, 38, 44] whereas studies on the impact of recurrent stroke has so far been negative. One of the reasons for this may be that smoking cessation is effective post-stroke and, consequently, baseline smokers turn into non-smokers, and their risk of mortality and vascular events decreases after some years.[81]

In the general population, lots of evidence suggests that low social support is an important risk factor for all-cause mortality.[82, 83] Few studies have examined the association with stroke, but recently a large epidemiological study from the US showed an independent association between a small social network and an excess risk of incident stroke.[84] Association between low social support and mortality and vascular events has also been reported in patients with established coronary heart disease (CHD)[85] or at risk of atherothrombosis.[86] In contrast, there are few published studies on the potential association between social support and mortality and vascular events after stroke. A small study from Norway reported an association between living alone and mortality[87] and a study from the US demonstrated an association between social isolation and MI, recurrent stroke and/or death after ischemic stroke.[70]

Social support has been defined in various ways[83] and can be divided into structural and functional support. Structural support refers to the structure of the social network measured as number of close contacts or as living with a partner. Functional support is the support provided by the network and may consist of instrumental, financial or emotional support.[88] It is not clear which aspect of social support is most important for cardiovascular risk.[89] However, living with a partner, i.e. cohabitation status is a simple measure of social isolation, which has often been used as a proxy for social support.[86, 90]

Occupational class, education and income are often used as indicators of socioeconomic status. Globally, but also in Sweden,[91, 92] stroke incidence is higher in areas with low socioeconomic levels. An inverse association has been reported between socioeconomic status and mortality after stroke.[93, 94] However, low socioeconomic status is also associated with higher prevalence of risk factors such as smoking and hypertension as well as increased stroke severity.[95, 96] Results from studies taking into account these confounders are

contradictory.[94, 97] Less and conflicting evidence exists on an association between socioeconomic status and stroke recurrence.[98]

A meta-analysis has concluded that moderate and high physical activity is associated with reduced risk of ischemic stroke[99] and regular physical activity is recommended in clinical guidelines for secondary prevention after stroke.[100] Yet, surprisingly few studies have investigated the influence of pre-stroke physical activity on outcomes after ischemic stroke. Some studies have reported that prestroke physical activity is associated with better short- and long-term functional outcome, but not with fewer vascular events.[101, 102] It has been suggested that the effect of physical activity may partly be mediated by less severe strokes in people being physically active.[103]

The results from a meta-analysis of published observational studies on the relationship between alcohol consumption and incident stroke, indicate that heavy alcohol consumption increases the risk of ischemic stroke whereas light or moderate intake may be protective.[104] Alcohol consumption is difficult to estimate, as patients frequently underreport consumption in questionnaires.[105] Studies including only young ischemic stroke patients have reported an association between heavy drinking and long-term mortality.[41, 42, 87] Data on the influence in patients of all ages and on recurrent stroke is very limited, as alcohol intake seldom is included among baseline variables. However, Putaala et al found no association to recurrent stroke 5 years after ischemic stroke.[25]

### Comorbidities

Cardiac disease (CHD and congestive heart failure) is a robust risk factor of mortality after ischemic stroke in all ages.[41, 42, 44, 48, 74, 77, 87] A study including both variables[41] concluded that heart failure seems to be the cardiac factor particularly related to mortality, also supported by a high long-term mortality among patients with heart failure (around 20% after 1 year and 40% after 3 years).[106, 107] Despite that heart failure with low ejection fraction is a high-risk source of embolic stroke, cardiac disease has not been shown to predict recurrent stroke after ischemic stroke.

Atrial fibrillation is a major risk factor for stroke and was also associated with mortality, but not recurrent stroke in some long-term follow-up studies after ischemic stroke.[47, 108] This applies in particular to studies conducted in the 90's and increased mortality may partly be due to a low rate of anticoagulant therapy at discharge and a high early case fatality.[38] However, atrial

fibrillation was not a risk factor for mortality in studies including stroke subtype, probably because the largest etiology in CE stroke is atrial fibrillation, i.e. it is partly the same measure.

Follow-up studies frequently exclude patients with previous stroke or TIA, but those patients have a higher risk of mortality and of recurrent stroke compared to those with first-ever stroke. Moreover, previous stroke was also an independent predictor of a second recurrence after a first stroke recurrence.[109] Peripheral artery disease (PAD), which can be regarded as a marker of generalized atherosclerotic disease, has also been associated with long-term mortality after ischemic stroke.[41]

Obviously, one may assume that stroke patients with concomitant chronic diseases have increased mortality over time, and for example active tumour disease and impaired kidney function have been reported as independent predictors of mortality in young stroke patients.[41, 42, 110]

A recent meta-analysis concluded that post-stroke depression probably has an impact on mortality in medium-long follow-up (2-5 years).[111] In addition, depression pre-stroke is a major predictor of post-stroke depression.[112] Thus, it is plausible that pre-stroke depression also impacts mortality after stroke. A study from China also reports an association not only with mortality, but also with recurrent stroke.[74] However, few long-term follow-up studies have evaluated pre-stroke depressive symptoms in relation to post-stroke outcomes.

## Medication

Randomized clinical trials have shown the benefit of anticoagulants, statins, antihypertensive, and antiplatelet agents as secondary prevention after ischemic stroke.[113] However, evaluating medication after stroke in follow-up studies is complicated as to some extent, different stroke subtypes should have different secondary preventive medication. Moreover, to use “medication at discharge” as a measure of secondary medication is probably misrepresentative in long-term follow-up studies, as secondary preventive medication usually is administered in accordance to guidelines, whereas compliance may be poor after discharge. However, a recent large meta-analysis showed association between statin therapy at the time of stroke onset and reduced risk of death at 1 year.[114] A limitation was that in most of the included studies, the benefit of statins was not seen after adjustments for risk factors. The meta-analysis also concluded data to be more conflicting regarding the influence of post-stroke statin treatment. In addition, conflicting results were reported from two recent studies, not included in the

meta-analysis. One found a protective effect of statin usage at discharge[27], but the other showed no association with discontinuation of statins, both assessing recurrent events.[53] These studies also evaluated other pharmacological agents and found an association with improved survival and prescription of antiplatelet-, anticoagulant-, and angiotensin-converting enzyme inhibitors at discharge and with recurrent stroke and discontinuation of antiplatelet- and antihypertensive therapy.

### Stroke severity

Stroke severity is a well-established predictor of mortality in short-term follow-up after ischemic stroke.[38] The influence of stroke severity on long-term mortality is less pronounced, but association has been shown in several studies including all ages.[36, 44, 68, 74, 76] Conflicting findings have been reported in young stroke.[41, 42, 115] Data are limited for long-term studies of recurrent stroke as the majority have not included stroke severity as a baseline variable, however, two studies reported no association.[25, 27]

### Stroke subtype

The underlying mechanisms and risk factor profile vary according to stroke subtype[116, 117] and thus it may be expected that the etiologic stroke subtypes also have different risks of mortality and vascular events. Classification according to stroke subtype has been done in most recent, large studies in stroke patients under the age of 50 years, and has shown increased mortality for the subtypes CE stroke and LVD.[27, 41, 115] In studies in all ages, subtype often has been neglected and therefore data is more limited. Moreover, conflicting data have been published. Similar to results in young stroke studies, a study from Greece reported increased mortality in CE stroke compared with LVD[27] and a study from Korea reported increased mortality in all subtypes compared with SVD, with the worst prognosis for CE stroke.[36] However, regarding SVD the results are contradictory as SVD was associated with poorer long-term survival compared to other stroke subtypes in a study from Finland.[44] There are also indications of an attenuating effects of the favourable prognosis of lacunar stroke over time. According to a review including 27 cohort studies the risk of death was fourfold higher for non-lacunar compared to lacunar stroke the first month after index stroke, but thereafter decreased and was less than twofold higher for non-lacunar stroke after 1-5 years.[118]

Similar to mortality studies, the influence of stroke subtype on long-term recurrent stroke, has mainly been investigated among young stroke patients.



Two studies used multivariable modelling and one showed increased risk of stroke with the subtype LVD,[25] whereas there was only a pronounced trend in the other study toward higher recurrent stroke rate in the LVD group.[53] Scarce information is available for stroke in all ages. Only one study has investigated stroke subtype taking into account other relevant risk factors in the long-term perspective, but showed no impact on recurrent stroke.[27]

### **Predictors of coronary events**

The American Heart Association/American Stroke Association from 2012, suggests that some specific stroke subtypes, in particular LVD, carry a high risk of subsequent coronary events.[119] However, a systematic review from 2005 concluded that data was too sparse to draw any conclusions about the impact of subtypes on MIs after ischemic stroke.[118] After this review, two additional studies have investigated the influence of subtypes on subsequent coronary events after ischemic stroke. The first study, from Manhattan, found CE stroke to be an independent risk factor of a combination of MI and vascular death.[54] However, MIs accounted for a small proportion of the vascular deaths in this study, and the result could have been influenced by CE stroke having a high mortality rate. The second study, from Greece, reported that the subtypes SVD and CE stroke had a lower risk of MI compared with LVD.[27]

To the best of our knowledge there is only one study after ischemic stroke with  $\geq 5$  years follow-up, reporting independent predictors of coronary events.[27] Furthermore, independent predictors have been reported from two Swedish studies, including also hemorrhagic stroke,[57, 120] and CHD and heart failure were independent predictors in these studies. The FUTURE study from the Netherlands also investigated predictors of coronary events, but only took into account age and gender in the analysis.[35] To conclude, data on predictors of coronary events after ischemic stroke is limited and the impact of subtypes are not fully elucidated.

### **Predictors of functional outcome**

In long-term follow-up studies including both ischemic and hemorrhagic stroke, increasing age and a high initial stroke severity have consistently been independently associated with impaired functional outcome.[62, 64, 121, 122] As expected, recurrent events also showed association with worse outcomes in studies including this as a covariate.[62, 64, 121] Significant cognitive problems

were associated with dependency (mRS >2) among stroke survivors in a population based study,[65] and post-stroke epilepsy showed association to poor functional outcome in the FUTURE study, including only young stroke patients.[121] To summarize, few studies have investigated independent predictors of long-term functional outcome after stroke, and in particular after ischemic stroke and thus, the knowledge is limited.

### **Cognitive dysfunction after ischemic stroke**

In young and middle-aged stroke patients, cognitive dysfunction/mild cognitive impairment, is a major concern, whereas the prevalence of post-stroke dementia in this age group is low. Cognitive dysfunction has major consequences as it affects social functioning, return to work and quality of life.[123-125] However, there is uncertainty and overlap between cognitive dysfunction and dementia, and between cognitive dysfunction and normal cognitive function, and there is no consensus on the exact criteria for cognitive dysfunction.[126-128] The usage of different screening methods with different cutoff levels, and different neuropsychological batteries, along with age variation, may explain why studies have estimated a huge variation in the prevalence of cognitive dysfunction in long-term follow-up after ischemic stroke (35%-79%).[125, 129-132] There is much debate as to which test is the most appropriate for detecting cognitive dysfunction after stroke and if the existing screening tools are sensitive and specific enough for use after stroke.

#### **Screening tests for cognitive dysfunction after stroke**

The Mini-Mental State Examination (MMSE)[133] is the most widely used test for assessing cognitive dysfunction after stroke.[126] However, the MMSE was designed for detection of dementia due to Alzheimer disease and may be insensitive in detecting mild post-stroke cognitive dysfunction.[134] Further, the test result is dependent on both age and education.[135] Other limitations with the MMSE are the well-known ceiling effect and the tendency to overestimate dysfunction in patients with aphasia. Moreover, executive functions, which often are impaired after stroke, are not examined with the MMSE.[136, 137] Nor is it clear what the cutoffs should be used for detecting dementia and mild cognitive dysfunction.

The Montreal Cognitive Assessment (MoCA) has received increasing attention in recent years as a screening test for cognitive dysfunction after stroke. In the original MoCA study, the sensitivity was 100% and the specificity 87% for

detecting cognitive dysfunction as assessed by neuropsychological testing, using the cutoff  $<27$ . [138, 139] Further benefits described compared with the MMSE are inclusion of items assessing executive functions and attention, and inclusion of more complex memory and language tasks. [131] However, the test has also been criticized, and was reported to be no more sensitive than the MMSE in screening cognitive deficits, compared with a neuropsychological test battery. [140]

The MMSE and the MoCA are the most commonly used screening tests for cognitive dysfunction after ischemic stroke. However, other screening tests have also been used i.e. the R-CAMCOG, [141] the Addenbrooke's Cognitive Examination-Revised (ACE-R), [142] and the cognitive Functional Independency Measure (FIM). [143]

The Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS) was constructed for providing a rapid, reliable and valid screening of different cognitive domains. [144] It is also intended to give qualitative aspects of performance. The construct and validity has been examined both in the Swedish population and in a group of patients from a neuro-rehabilitation clinic including stroke patients. [145, 146] However, the utility of the BNIS as a screening instrument for cognitive dysfunction in long-term follow-up after ischemic stroke has not been investigated.

## AIM OF THE THESIS

The overall aim of this thesis is to increase our knowledge on long-term outcome in young and middle-aged ischemic stroke sufferers. In these studies of adult patients with ischemic stroke before 70 years of age the specific aims were:

- To investigate predictors of functional outcome and recurrent vascular events with special focus on etiologic subtypes in 2-year follow-up.
- To explore the utility of the cognitive screening instrument the Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS) in long-term follow-up.
- To investigate the influence of living alone on long-term mortality, taking into account conventional vascular risk factors, stroke subtype and social confounders.
- To describe the incidence of recurrent vascular events in this cohort compared to a healthy control group and to identify predictors of recurrent vascular events in cases.

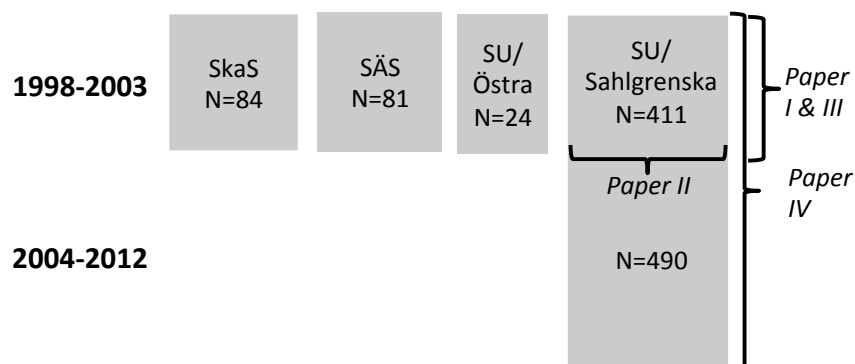
## SUBJECTS AND METHODS

### The Sahlgrenska Academy Study on Ischemic Stroke – SAHLSIS

For the purpose of investigating genetic and hemostatic factors in ischemic stroke, our group initiated a large case-control study, the Sahlgrenska Academy Study on Ischemic Stroke (SAHLSIS), [116] which constitutes a well characterized sample of ischemic stroke patients and healthy controls from Western Sweden.

#### Patients

The study population comprised patients who participated in SAHLSIS. Six hundred white patients who presented with first-ever or recurrent acute ischemic stroke before 70 years of age were recruited consecutively at four Stroke Units in Western Sweden between 1998 and 2003. Thereafter patients were continuously recruited at the Stroke Unit at the Sahlgrenska University Hospital/Sahlgrenska in Gothenburg. By April 1, 2012 1090 patients had been included in SAHLSIS (Figure 1).



**Figure 1.** Patients according to inclusion site. SkaS indicates Skaraborgs Sjukhus; SÄS, Södra Älvsborgs Sjukhus; SU Sahlgrenska Universitetssjukhuset.

All patients were included within 10 days from the index stroke. The inclusion criteria were 1) acute onset of clinical symptoms suggestive of stroke and 2) CT scan or MRI of the brain without hemorrhage. Patients were excluded if 1) they were younger than 16 or older than 69 years 2) the following evaluation showed

an etiology other than ischemic stroke 3) they had a diagnosis of cancer of advanced stage, infectious hepatitis or HIV.

## Controls

Six hundred white controls were recruited to match the first 600 cases with regards to age, gender and geographical residence area. The controls were randomly recruited from a population-based health survey[147] or from the Swedish Population Register (Skaraborg and Älvsborgs residents, and controls younger than 30 years). The exclusion criteria were history of stroke, CHD, or PAD. In total 1,107 controls were contacted. Of those, 208 did not respond, 191 were unwilling to participate and 108 fulfilled the exclusion criteria.

### *Methodological considerations*

The study is based on hospitalized cases. However, the stroke admission rate in Sweden is high, with 87-95%[91, 148] of the cases <75 years being admitted to hospital, and the case-fatality rate is low, especially in the age group studied here. Therefore it is unlikely that a patient selection bias has influenced our results. The controls were recruited by random sampling from the general population in the same geographical area as patients and were excluded if they had cardiovascular disease according to the prespecified exclusion criteria. Thus, as a comparison group, the controls do not reflect the whole population, but are likely to have lower mortality- and vascular event rates.

SAHLSIS includes participants younger than 70 years and the results are obviously only representative for this age group.

Both patients with first-ever and recurrent stroke are included in SAHLSIS, and this may influence the results. Thus, separate analyses have been done in paper I and IV, including only patients with first-ever stroke.

## **Baseline data**

### Assessment at baseline and risk factor definitions

The first 600 cases were examined both in the acute stage (day 1-10 after the event) and at a follow-up visit at 3 months. The following 490 cases were examined only in the subacute phase after inclusion. Controls were examined once. The collection of baseline data has been described in more detail previously.[116, 149, 150] The protocol included questionnaires, anthropometrics, standardized blood sampling and measurements of blood pressure. The questionnaires included questions about demographic

characteristics, vascular risk factors, socioeconomic factors, life-style factors and co-morbidities and referred to the situation before the index stroke.

Initial stroke severity was assessed with the Scandinavian Stroke Scale (SSS)[151] for the first 600 patients. Thereafter, stroke severity was assessed from medical records using the National Institutes of Health Stroke Scale (NIHSS).[152] It should be noted that the SSS differs in the direction of measurement compared to the NIHSS, e.g. no impairment is 58 of 58 in the SSS and 0 of 42 in the NIHSS. For paper II-IV, the SSS scores were converted to NIHSS by a mathematic equation.[153]

Hypertension was defined by pharmacological treatment for hypertension or systolic blood pressure  $\geq 160$  mm Hg and/or diastolic blood pressure  $\geq 90$  mm Hg. Diabetes mellitus was defined by diet or pharmacological treatment, fasting plasma glucose  $\geq 7.0$  mmol/L, or fasting blood glucose  $\geq 6.1$  mmol/L. Hyperlipidemia was defined by pharmacological treatment or total fasting serum cholesterol  $> 5.0$  mmol/L, and/or LDL  $> 3.0$  mmol/L. Smoking history was coded as current versus never or former (smoking cessation at least one year prior to inclusion in the study). Waist-hip-ratio (WHR) was defined as waist divided by hip circumference and it was categorized as low, normal (reference), moderate and high with gender-specific cutoffs as defined by the World Health Organization (for men:  $< 0.85$ ,  $0.85 - < 0.95$ ,  $0.95 - < 1$  and  $\geq 1$ ; and for woman:  $< 0.7$ ,  $0.7 - < 0.8$ ,  $0.8 - < 0.85$  and  $\geq 0.85$ ).[154] Obesity was defined as body mass index  $\geq 30$ . [155]

Occupational class before index stroke was coded according to the Swedish socioeconomic classification system.[156] Employed and self-employed professionals, higher civil servants, executives and intermediate non-manual employees formed one category, and all others formed a second category. Sedentary leisure time was coded as low if moderate physical activity was performed at less than 4 hours per week, otherwise moderate/high. Alcohol consumption was coded as 4 times a week versus  $< 4$  times a week or never. Cohabitation status was categorized as living with a partner or an adult family member versus living alone. Cohabitation status for patients was also confirmed by medical records.

Personal history of stroke was obtained from questionnaires and medical records. Personal history of CHD was defined as self-reported history or information from medical records: 1) MI or by-pass surgery or percutaneous coronary intervention (paper I, III and IV) or 2) ECG changes indicating

previous MI (only in paper I). Atrial fibrillation was identified on ECG during the hospital stay or by medical history from the questionnaire.

Hypertension, diabetes, hyperlipidemia, obesity, smoking, leisure-time physical inactivity, personal history of stroke, personal history of CHD, and atrial fibrillation were considered as well-documented risk factors in line with current evidence.[72] In paper IV a risk factor score was constructed and patients were divided into 3 groups:  $\leq 1$ , 2-3, and  $\geq 4$  risk factors.

### *Stroke subtyping*

The TOAST system[13] was used for stroke subtyping, with slightly modified criteria.[150, 157] Examination in the acute stage was done by a physician trained in stroke medicine. Neuroimaging with either CT or MRI was done in all cases. Other investigations were performed when clinically indicated (Table 3).

**Table 3.** Investigational work-up for cases (n=1,090).

Investigational work-up	Number (%)
Computer tomography	1082 (99)
Magnetic resonance imaging	690 (63)
Magnetic resonance angiography	383 (35)
Cerebral angiography	117 (11)
Extracranial carotid ultrasound	812 (74)
Transcranial duplex ultrasound	204 (19)
Transthoracic eco-cardiography	754 (69)
Transesophageal eco-cardiography	562 (52)

SVD was defined as a clinical lacunar syndrome with a relevant infarction of  $<15$  mm or normal CT/MRI in the absence of both CE source and LVD source. LVD was defined as stenosis (corresponding to  $>50\%$  diameter reduction according to NASCET criteria) or an occlusion of a clinically relevant precerebral or cerebral artery, presumably due to atherosclerosis. LVD also included cases with  $>4$ mm large plaque in the aortic arch. Potential sources of cardiac embolism should be excluded. CE stroke was defined as the presence of atrial fibrillation, sick sinus syndrome, MI in the past 4 weeks, cardiac thrombus, infective endocarditis, atrial myxoma, prosthetic mitral or aortic valve, valvular vegetations, left ventricular akinetic segment, dilated cardiomyopathy, or patent foramen ovale in combination with either atrial septal aneurysm, deep venous thrombosis or prothrombotic disorder. LVD source should be excluded. Cryptogenic stroke was defined when no cause was identified despite of an extensive evaluation. Other determined cause of stroke included arterial dissection, vasculitis, hemathologic disorders, monogenic



syndroms and complications of cardiovascular procedures. Undetermined stroke included cases for whom more than one etiology was identified, or when evaluation was cursory.

#### *Methodological considerations*

If a high proportion of the patients had divorced or become widows/widowers or had begun cohabiting during the long-term follow-up, this could have influenced our results. Therefore we checked cohabitation status 3 months and 7 years after index stroke. Only 2 patients had changed cohabitation status at 3 months. After 7 years, 439 (84%) of the surviving patients were eligible for follow-up through questionnaires, of which 9% had changed cohabitation status: 4% had become widows/widowers, 4% had divorced and 1% had begun cohabiting. Thus, most patients changed to the living alone group, and if anything this could have diluted our results. However, the majority of deaths occurred before the 7-year follow-up and we have no information on those patients.

TOAST is the most commonly utilized system for the classification of etiologic subtypes of ischemic stroke. Other more recently developed classification tools are the Causative Classification System (CCS) and the A-S-C-O (A for atherosclerosis, S for small vessel disease, C for Cardiac source, O for other cause). However, in all of these schemes there is room for interpretation.[158]

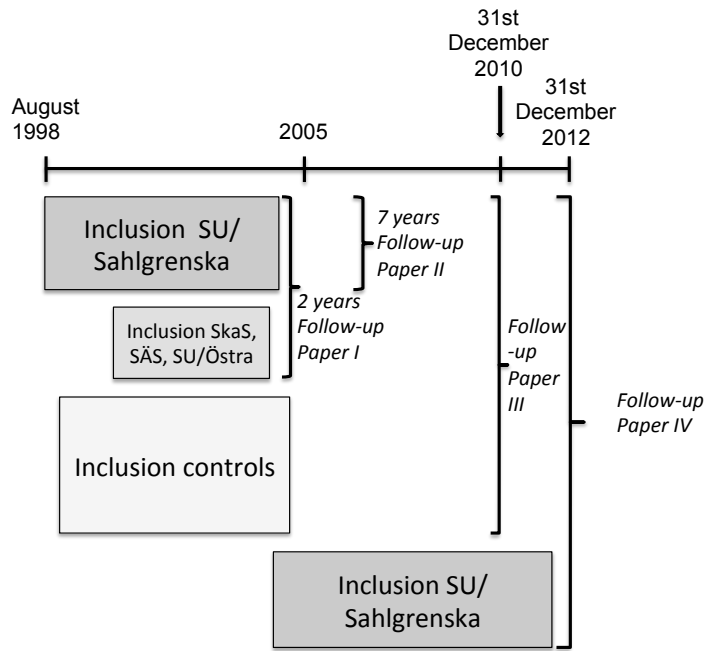
## **Follow-up**

### General design Study I-IV

The general outline of the longitudinal studies within SAHLSIS is schematically depicted in Figure 2. Follow-up was conducted 2 years after the index stroke in study I, after 7 years in study II, 31<sup>st</sup> December 2010 in study III and 31<sup>st</sup> December 2012 in study IV.

### Cause of Death

We used the unique 10-digit Swedish person identity number assigned to all Swedish Citizens, to identify non-survivors from the Swedish Total Population Register (Folkbokföringen). For all non-survivors, cause of death was obtained from the Swedish Cause of Death Register, which contains data on underlying cause of death. It is based on International Classification of Diseases version 10



**Figure 1.** Study populations and timing of follow-up in the studies. SKaS indicates Skaraborgs sjukhus; SÄS, Södra Älvsborgs sjukhus; SU Sahlgrenska universitetssjukhuset.

(ICD-10). In order to determine the cause of death with even greater accuracy, we also reviewed all available medical records 6 months prior to death by using the Swedish Hospital Discharge Register (the National Patient Register), both for patients dying at home and at hospital. By this procedure, 11% of underlying cause of death was changed compared with the Swedish Cause of Death Register. Further, cause of death was categorized into vascular deaths and non-vascular deaths. The following ICD-10 codes were used for vascular death: I10-I28, I42-I50, I60-I89 and F01. Death was also considered to be vascular if it occurred within 30 days of a major stroke or an MI.

*Methodological considerations*

In this study, this procedure resulted in 20 changed causes of death, of which 65% was changed due to additional findings in the medical records and 35% because the diagnosis in the cause of death register was very specific and there were no supportive findings in the medical records. Of a note is that we could verify all cancer diagnosis in the medical records.

## Recurrent events

We searched the Swedish Hospital Discharge Register for fatal and non-fatal recurrent strokes, fatal and non-fatal coronary events and other arterial thrombotic events. First, we did a broad search for respective events and surgical procedures in the Swedish Hospital Discharge Register. Thereafter, we confirmed the events and the procedures by reviewing the corresponding medical records. We changed diagnosis in 10% of the cases after having scrutinized the corresponding medical record. This was usually the result of an old event being incorrectly classified as a new event or a clear typographical error in the Swedish Hospital Discharge Register. If we were unable to find the medical record (15%), we registered the event if it was the main diagnosis or the main surgical procedure.

Stroke was defined as an episode of focal neurological deficits with acute onset and lasting >24 hours or resulting in death and included ischemic stroke, hemorrhagic stroke and subarachnoid hemorrhage. When occurring adjacent to index stroke, the new neurological deficit had to occur after >24 hours of neurological stability and could not be attributable to edema, hemorrhagic transformation or concomitant illness. We searched the diagnoses I60.0-I69.8 in the Swedish Hospital Discharge Register.

TIA was defined in the same way as stroke, but had to have resolved completely within 24 hours. The following discharge codes were evaluated: G45.0-G45.9. This endpoint was only included in paper I. In paper IV, where the follow-up was longer, we chose to exclude TIA as an endpoint, as not all TIAs are recognized by the patients.

A coronary event was defined as a fatal or non-fatal MI, acute or elective percutaneous coronary intervention or coronary artery bypass grafting. MI was defined as markers of myocardial ischemia with at least one of the following: symptoms of ischemia, ECG changes indicative of new ischemia or imaging evidence indicative of new ischemia.[159] We reviewed the medical records with the ICD-10 codes I21.0-I22.9 for MI and the surgical procedures FNG00-FNG96 for percutaneous coronary intervention and FNA00-FNF96 and FNH00-FNW98 for coronary bypass grafting. In paper I we also included hospitalization for unstable angina and excluded elective coronary procedures in the definition, however, no such events occurred within the follow-up period.

Another arterial thrombotic event was defined as an endovascular or surgical procedure aimed to remove a thrombosis or an embolus in a peripheral artery or

a surgical amputation due to critical ischemia. We reviewed medical records with the following codes: XPX99, FAB10, PBE10-PBF99, PCE30-PCF99, PDE10-PDF30, PEE10-PEF12, PFE10-PFE30, NFQ19, NFQ99, NGQ19, NGQ99, and NHQ11-NHQ17.

The composite outcome in study I consisted of any of fatal and non-fatal stroke, TIA, MI, unstable angina or death. In study IV only permanent vascular events were registered and these included fatal and non-fatal stroke, coronary event or another thrombotic event (i.e. procedures for PAD).

#### *Methodological considerations*

Our follow-up of recurrent events was based on diagnoses in the Swedish Hospital Discharge Register, which have been shown to have a sensitivity of a stroke diagnosis of 88% in a study from Örebro.[160] The recurrence rates based solely on this register may therefore be underestimated. The reason for this could be that patients with acute stroke are not always being hospitalized and patients living at institutions and nursing homes are sometimes not admitted to hospital despite suffering of symptoms of stroke. However, in the first study we also performed a structured interview with the patients after 2 years, with questions about symptoms of recurrent stroke, TIA and MI. By this procedure we only found one additional TIA. Moreover, our patients are almost 20 years younger compared with the patients in the Örebro study, and only a small percentage lives at nursing homes. Thus it is likely that the recurrence rates in our studies reflect the true rate fairly well.

In study I, our aim was to study a composite outcome consisting of all cerebral and coronary events, both ischemic and transient. However, only fifteen patients suffered a TIA and no patient had unstable angina within 2 years. Swedish National Guidelines for Stroke Care stated 2005 the need of inpatient care of TIA patients, but in the beginning of SAHLSIS, probably not all patients with TIA were hospitalized. However, as described before, we just found one more TIA patient with interviews. Yet, uncomplicated TIA patients may not have sought medical help at all.

In study IV, as follow-up was longer, we decided to include only permanent vascular events in the composite outcome. Therefore, we also included procedures for PAD.

#### Functional outcome

In study I, patients were contacted after 2 years by a study nurse trained in stroke medicine. A structured telephone interview was performed and functional

outcome was assessed by the mRS.[161-163] Five percent of the patients were unable to provide an answer and in these cases a relative or a caregiver were interviewed. The mRS score was dichotomized into favourable outcome (score 0-2) versus poor outcome (death or dependency, score 3-6). The mRS is described in Table 4.

**Table 4.** Description of the modified Rankin Scale.

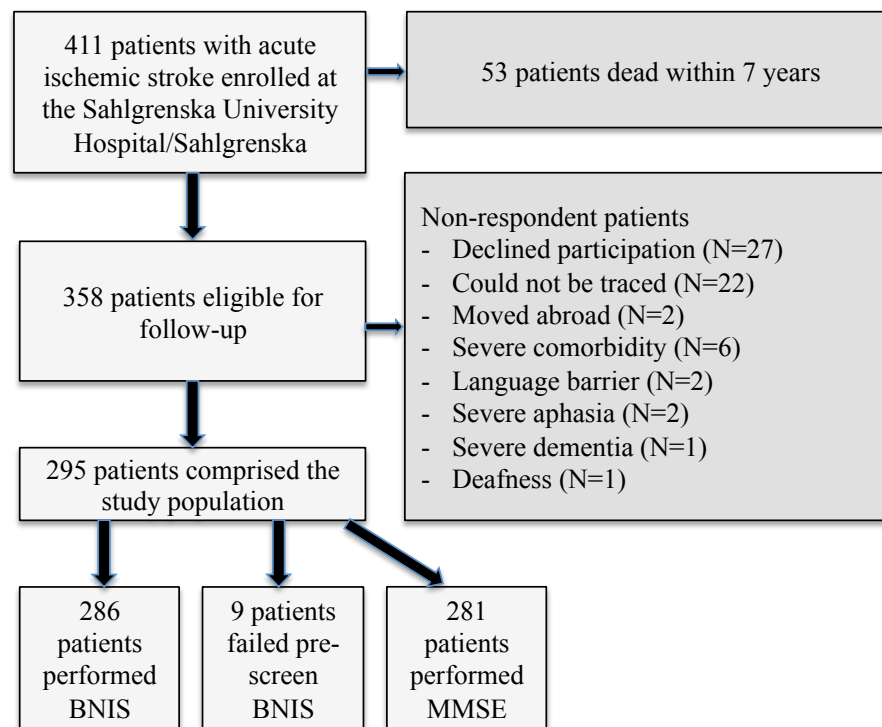
The modified Rankin Scale	
Description	Score
No symptoms at all	0
No significant disability despite symptoms; able to carry out all usual duties and activities	1
Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance	2
Moderate disability; requiring some help, but able to walk without assistance	3
Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance	4
Severe disability; bedridden, incontinent and requiring constant nursing care and attention	5
Dead	6

## Follow-up study II

All patients included at the Stroke Unit at the Sahlgrenska University Hospital between 1998 and 2003, who were alive after 7 years (n=358), were invited to participate in a follow-up with focus on cognition. The study population and the non-respondents are shown in Figure 3. The study protocol included a questionnaire and two visits: 1) to the study nurse and 2) to a study neurologist. Patients who were unable to visit our clinic were offered a home visit by the study nurse and one study neurologist.

### *Assessment*

The study nurse administered the cognitive screening instrument the BNIS and evaluated functional outcome by the mRS at the first visit. The study nurse was trained in administering the BNIS and was supervised throughout the study by a neuropsychologist (Caisa Hofgren). The BNIS test was developed to assess cognitive function in a neurological setting. It should reflect a variety of cerebral functions and give qualitative aspects of performance.[164, 165] The test normally takes 15-20 minutes to administer. It has the form of a booklet and contains 19 cards with 37 items in all. The BNIS comprises a pre-screen (level of arousal 3p, basic communication 3p and co-operation 3p) to evaluate whether



**Figure 2.** Flowchart over the recruitment and the study population in study II. BNIS indicates Barrow Neurological Institute Screen for Higher Cerebral Functions; MMSE, Mini-Mental State Examination; N, number.

the patient is capable to take in further testing. The total score (maximum 50 points) reflects the overall cognitive function and consists of the result from the pre-screen and the 7 subscales. The subscales are speech and language, orientation, attention/concentration, visuospatial and visual problem-solving, learning and memory, affect, and awareness, for a description of the included items see Table 5.[145, 166] During the initial validation of the BNIS in healthy control subjects, the mean score was slightly over 46. Thus, the cutoff score to indicate possible cognitive dysfunction was set at <47 points. [145, 165] Moreover, the cutoff has been used to differentiate patients with diagnosis associated with brain-dysfunction from a control group.[146]

The MMSE was administered by a stroke neurologist at the second visit. The

**Table 5.** The Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS) items.

BNIS Items	Score	Subscale score
<i>Pre-screening</i>		
Level of consciousness	3	
Basal communication	3	
Cooperation	3	9
<i>Speech and language</i>		
Fluency	1	
Paraphasia	1	
Dysarthria	1	
Comprehension	2	
Naming	1	
Repetition	2	
Reading	1	
Writing – sentence copying	1	
Writing - dictamen	1	
Spelling - irregular	1	
Spelling - phonetic	1	
Arithmetic - number/symbol alexia	1	
Arithmetic - dyscalculia	1	15
<i>Orientation</i>		
Left-right orientation	1	
Place orientation	1	
Time orientation	1	3
<i>Attention/concentration</i>		
Arithmetic memory/concentration	1	
Digits - forward	1	
Digits - backward	1	3
<i>Visuospatial and visual problem-solving</i>		
Visual object recognition	1	
Constructional praxis dominant hand	1	
Constructional praxis non-dominant hand	1	
Visual scanning	2	
Visual sequencing	1	
Pattern copying	1	
Pattern recognition	1	8
<i>Memory</i>		
Number/symbol test	4	
Delayed recall	3	7
<i>Affect</i>		
Affect expression	1	
Affect perception	1	
Affect control	1	
Spontaneous affect	1	4
<i>Awareness</i>		
Awareness vs performance	1	1
<b>Total score</b>	<b>50</b>	

MMSE takes 5-10 minutes to administer, has a maximum score of 30 points and the items are grouped into subscales of orientation, registration, attention and calculation, recall and language, see Table 6. Cutoff levels suggested for screening for cognitive dysfunction in stroke patients have varied between less than 27 and less than 30.[140, 167, 168] In the present study, cutoff score less than 29 was chosen to achieve high sensitivity for the MMSE.[168]

The stroke neurologist also assessed stroke-related neurological deficits by NIHSS. The depression subscale of the Hospital Anxiety D Depression Scale was used to assess depression with a subscale score of greater than 10 indicating depression.[169]

Number of years in school was dichotomized according to the norms of the Swedish educational system, into “low level of education” (9 years or less) and “high level of education” (more than 9 years).

**Table 6.** Mini-Mental State Examination (MMSE), version used in the Sahlgrenska University Hospital Study on Ischemic Stroke.

MMSE Items	Score
<i>Orientation to time</i>	
Date	1
Month	1
Year	1
Day of week	1
Season	1
<i>Orientation to place</i>	
Hospital	1
Floor	1
City	1
County	1
State	1
<i>Registration (repeating prompt)</i>	
Key	1
Toothbrush	1
Lamp	1
<i>Attention and Calculation; serial sevens or if unable to do this, spelling "konst" backwards</i>	
"93"	1
"86"	1
"79"	1
"72"	1
"65"	1
<i>Recall</i>	
Key	1
Toothbrush	1
Lamp	1
<i>Language</i>	
Watch	1
Pencil	1
Repeat "No ifs, ands or buts"	1
<i>Complex commands</i>	
Three step command:	
Takes a paper in right hand	1
Folds paper in half	1
Puts paper in knee	1
"Close your eyes"	1
Writes a complete sentence	1
<i>Visuo Construction</i>	
Draws overlapping pentagram	1
Total score	30

*Methodological Considerations*

The cutoff level of the BNIS test of <47, based on the average score of healthy controls without cognitive dysfunction, has been used in other studies[145, 146] and we attempted to evaluate its validity for stroke. This cutoff proved to have high sensitivity (92%), but only moderate specificity (56%).[165, 170] However, the aim of the present study was to evaluate the usefulness of the BNIS as a screening instrument among ischemic stroke patients, which requires a high sensitivity.

The optimal method would have been to compare the BNIS with other neuropsychological testing, which would have been too time-consuming. Therefore we favoured a high sensitivity on both tests, with cutoff <47 on the BNIS, and <29 on the MMSE.

It has been reported that the result of the MMSE test is rather sensitive to both increasing age and educational level.[140, 171, 172] Likewise, in earlier studies[145, 146] as well as in paper II, the BNIS result was also associated with age and educational level. It is reasonable to presume that age and educational level affect both tests in a similar way. Therefore, even though we did not correct for these parameters *per*



*se*, their effects likely cancel each other out.

The study may have been subject to a certain selection bias, as patients who declined to participate in the follow-up (18% of the original cohort), had on average higher NIHSS scores at index, indicating more severe stroke, compared with participating patients. Thus, the proportion with cognitive dysfunction 7 years after stroke in the present study may be underestimated.

### **Statistical analysis**

Differences between groups were examined with the chi-square test for proportions or Fischer's exact test as appropriate for the categorical variables. One-way ANOVA or Student's t-test were used for the continuous variables. Non-parametric tests were used for differences between participating and non-participating patients in paper II. Kaplan-Meier survival analysis was used to estimate the cumulative incidence of mortality and recurrent vascular events, with corresponding 95% confidence intervals (CI) by follow-up time. The log rank test was used to compare rate estimates.

In paper I, multivariable Cox regression analyses with stepwise forward selection of predefined variables were done. In paper III variables with  $p < 0.1$  in the univariate analyses, as well as predefined possible confounding factors, were included in the multivariable Cox regression analyses. In paper IV, we constructed 2 sets of prediction models for each outcome and entered variables with  $p < 0.1$  from the univariate analyses. The missing values of the categorical variables were included as dummy variables in the Cox regression analyses.

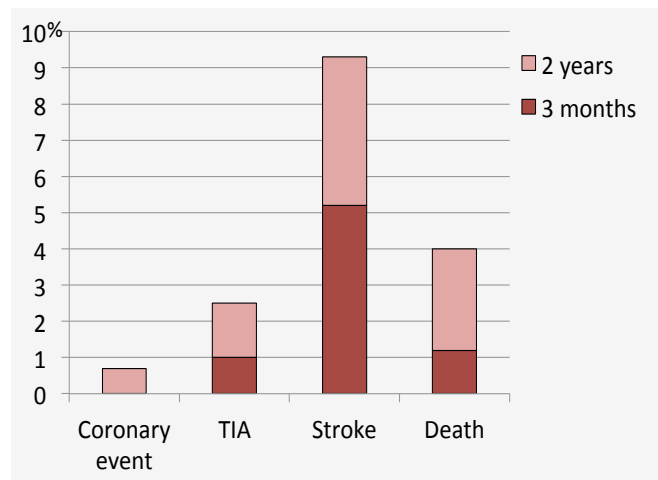
All statistical analyses were performed using SPSS for Windows version 18.0 and version 20.0. In addition, in paper III and IV, the assumption of proportional hazards was checked for each covariate through the cumulative sums of martingale residuals (ASSESS statement in the PROC PHREG analytical procedure in SAS statistical package 9.3, that estimates parameters in a Cox regression model procedure). To maintain the assumption of proportional hazards, selected variables were entered in the multivariable models as time-dependent. Statistical significance was set at  $p < 0.05$ . For details regarding statistical methods, please refer to the respective papers.

## RESULTS

### Stroke subtype predicts outcome in young and middle-aged stroke sufferers (Paper I)

#### General outcome

The proportions of patients with recurrent stroke, TIA, coronary event and death after 2 years are shown in Figure 4. Approximately half of all strokes and TIAs occurred within 3 months. Thirty percent died within 3 months.

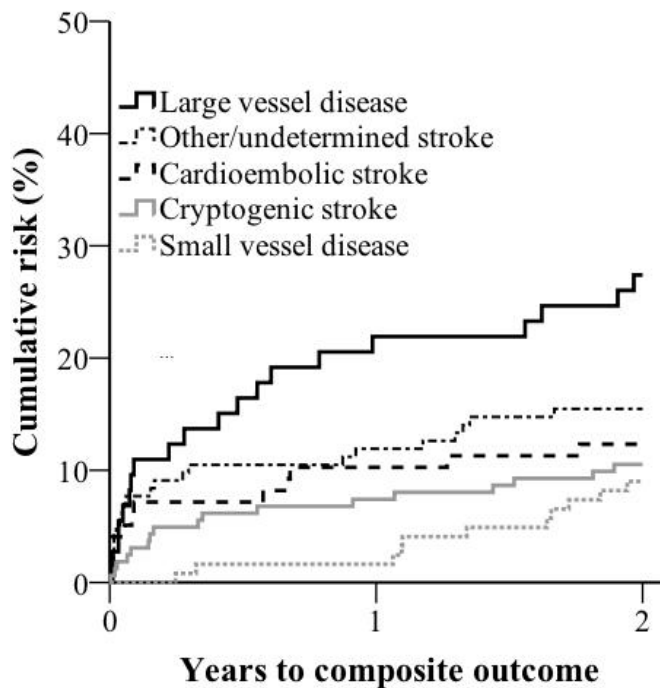


**Figure 3.** Coronary event, TIA, stroke and death after 2 years.

Seventy-one percent of deaths were due to vascular causes. There was a trend, although not statistically significant, towards fewer recurrent stroke and deaths among patients aged <50 years compared with those  $\geq$ 50 years (9 and 12% for recurrent stroke and 2 and 5 % for deaths respectively).

#### Composite outcome

Patients with LVD had 3 times higher cumulative risk of the composite outcome i.e. “recurrent stroke, TIA, MI, unstable angina and/or death”; 27% (95% CI, 17-38%) compared with patients with SVD 9% (95% CI, 4-14%), see Figure 5.

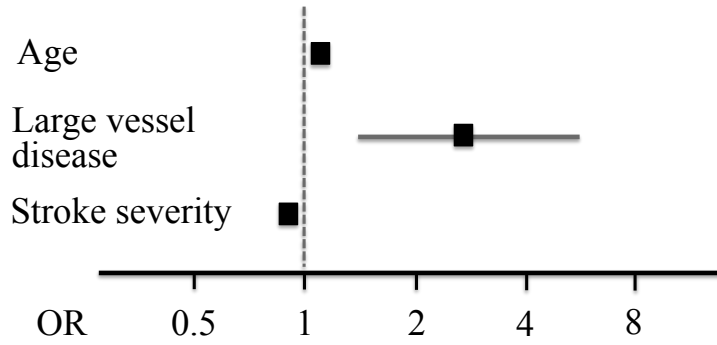


**Figure 4.** Cumulative risk of the composite outcome (Kaplan-Meier estimates) after 2 years, stratified by stroke subtype. Log rank  $p < 0.01$ .

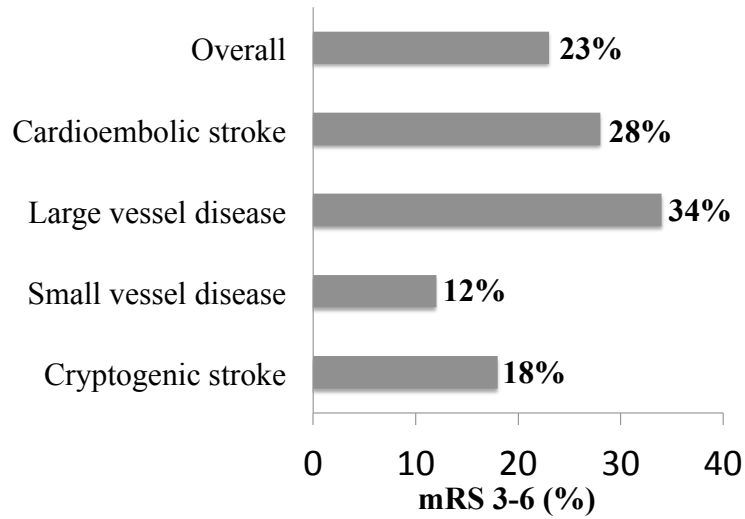
Predictors of the composite outcome in the univariate analyses were increasing age, stroke subtype LVD and stroke severity as measured by the SSS at index stroke and these associations remained in the multivariable analyses (Figure 6). Gender, diabetes, hyperlipidemia, hypertension and smoking were included in the stepwise logistic regression, but not selected in the final model.

#### Functional outcome

After 2 years 23% of the patients was dead or dependent (mRS 3-6). Functional outcome differed significantly between stroke subtypes,  $p < 0.001$ , Figure 7. The proportion with death or dependency was highest in the LVD group (34%), followed by CE stroke (28%) and other/undetermined stroke (27%). Patients with SVD had best functional outcome (82% mRS 0-2). In univariate analyses increasing age, stroke subtype LVD, CE stroke and other/undetermined stroke compared with SVD, diabetes and stroke severity at inclusion predicted death or dependency. Only age and stroke severity remained associated in the multivariable analyses and furthermore hypertension emerged as an independent



**Figure 5.** Adjusted Hazard Ratios (HRs) and 95% CIs for the composite outcome 2 years after index stroke. Stroke severity = Scandinavian Stroke Scale and the higher the score the less severe the stroke; HR therefore describes decreasing stroke severity.



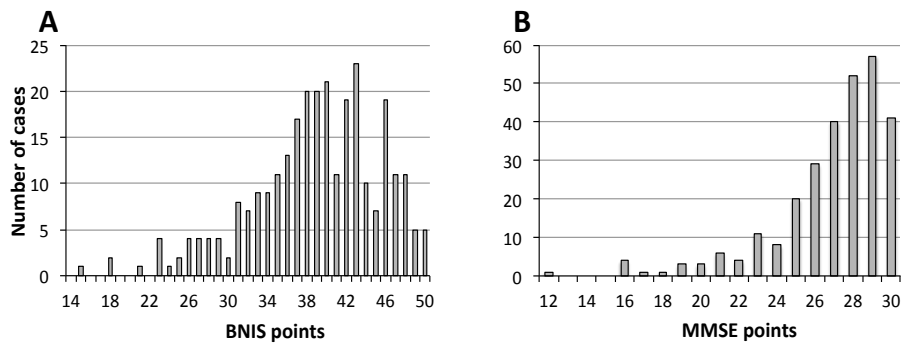
**Figure 6.** Death or dependence (mRS ≥ 3) according to stroke subtypes. Chi-square p < 0.001.

predictor (OR (95% CI) 1.0 (1.0-1.1) per year of age, 0.9 (0.9-0.9) for decreasing stroke severity and 1.8 (1.0-3.3) for hypertension). However, when stroke severity was excluded as a covariate, stroke subtype showed a significant

association with death or dependency, independent of age and vascular risk factors.

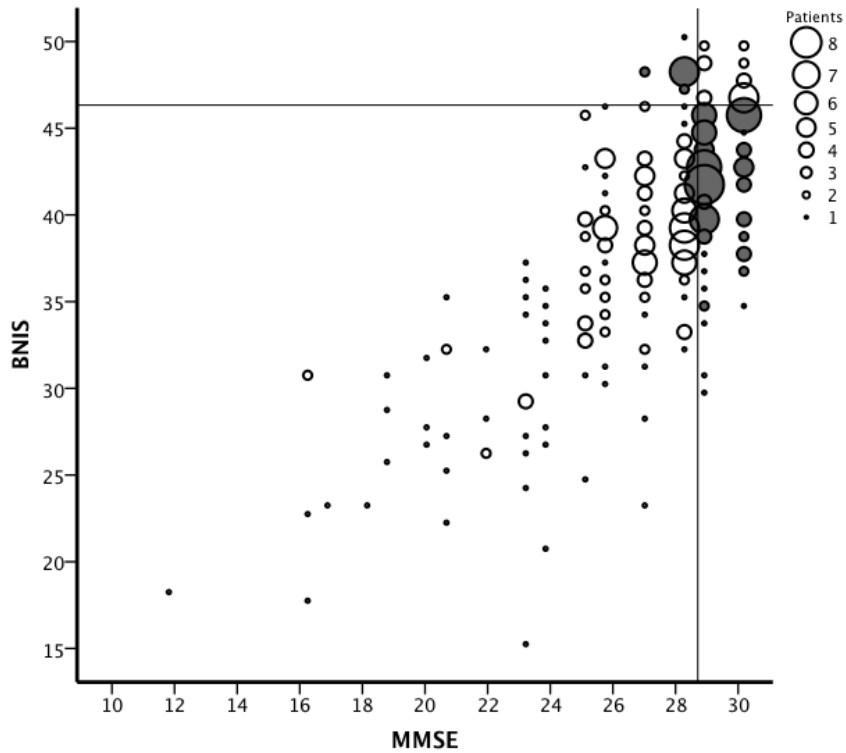
### The Barrow Neurological Institute Screen for Higher Cerebral Functions in cognitive screening after stroke (Paper II)

In this study we evaluated the BNIS and the MMSE as screening instruments after ischemic stroke. The BNIS scores were almost normally distributed whereas the MMSE scores were skewed towards top scores (Figure 8).



**Figure 7.** Histograms for BNIS scores (A) and for MMSE scores (B). Kurtosis and skewness were .58 and -.76 for BNIS and 3.9 and -1.8 for MMSE. BNIS indicates Barrow Neurological Institute Screen for Higher Cerebral Functions; MMSE, Mini-Mental State Examination.

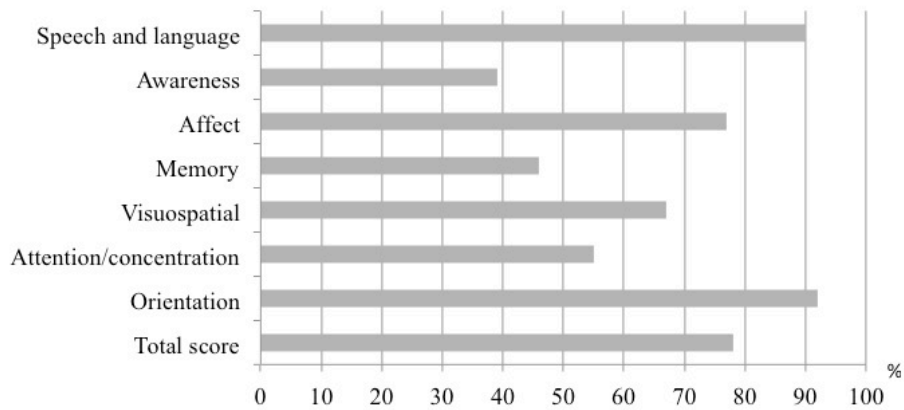
A possible cognitive dysfunction was detected among 89% according to the BNIS score (BNIS <47) whereas a lower proportion, 65%, had a MMSE score below cutoff (<29). Seventy-nine percent of the patients who were identified as non-impaired by the MMSE, were classified as having a possible cognitive dysfunction with the BNIS. Of the patients classified as impaired by the MMSE only 6% were classified as non-impaired by the BNIS (Figure 9). Both the MMSE and the BNIS correlated with mRS (Spearman rho = -.40 and -.48,  $p < 0.001$  for both). All patients with normal BNIS scores were independent according to the mRS (mRS score 0-2). Six percent of the patients with normal MMSE were dependent according to the mRS. The BNIS score was associated with age, educational level, depression and number of strokes ( $p < 0.001$  for all). Similar associations were detected for the MMSE score (all  $p < 0.001$ ), data not shown.



**Figure 9.** Bubble plot of BNIS total score versus MMSE total score. The horizontal line shows the cutoff used for BNIS and the vertical line shows the cutoff used for MMSE. Spearman rho =.65, p <0.01. The shaded bubbles represent patients with non-agreement between BNIS and MMSE in having possible cognitive dysfunction. BNIS indicates Barrow Neurological Institute Screen for Higher Cerebral Functions; MMSE, Mini-Mental State Examination.

### Cognitive profiles – the BNIS and the MMSE subscales

All BNIS subscales, except orientation and language, showed good qualities for screening purposes with respect to having no ceiling effect, mean performance around the midscale and good or acceptable properties for discrimination between subjects. High levels of cognitive dysfunction were found for the BNIS subscales attention, memory, visuospatial problem solving and awareness (Figure 10). In contrast, almost all of the MMSE subscales showed high mean scores and pronounced ceiling effects. Recall and repetition were the only subscales with mean performance less than 80 percent of maximum score (data not shown).



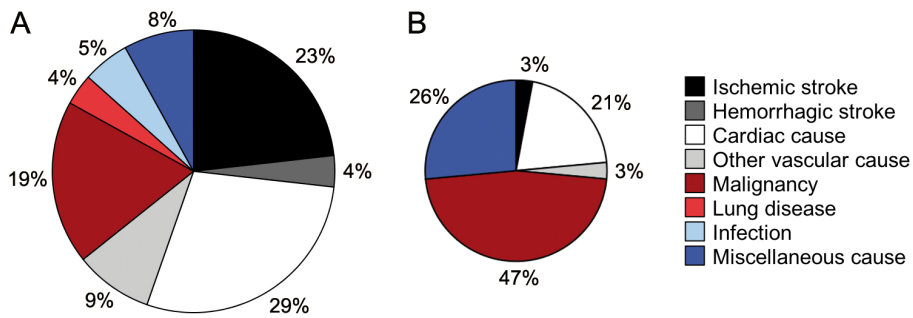
**Figure 10.** Cognitive profiles for the 186 patients. Bar chart of the subscales scores and the total score of the Barrow Neurological Institute Screen for Higher Cerebral Functions. The mean value in percentage of maximum score is displayed for each cognitive domain separately.

### **Impact of living alone on long-term mortality after ischemic stroke (Paper III)**

#### General outcome

Patients were followed for a median of 8.8 years (interquartile range (IQR) 7.7-10.0), in total 5,080 person years. Follow-up time for the controls was 8.2 years (IQR 7.7-10.0), in total 5,199 person years. During the follow-up period, 112 (19%) patients and 34 (6%) controls died, which corresponds to 22 and 7 deaths per 1,000 person years, respectively (log rank  $p < 0.001$ ). Cumulative mortality rates for patients were 2% (95% CI, 0.8-3%) at 1 year, 6% (95% CI, 4-8%) at 3 years, 10% (95% CI, 7-12%) at 5 years and 14% (95% CI, 11-17%) at 7 years. These rates were more than 4 times higher than the mortality rates of the age-and sex matched controls, who were free of cardiovascular disease at inclusion.

Causes of death for patients and controls are displayed in Figure 11. Sixty-four percent of deaths among patients and 26% of deaths among controls were due to vascular causes.



**Figure 11.** Causes of deaths for cases (Panel A) and controls (Panel B).

### The impact of living alone

Table 7 shows selected baseline characteristics for cases according to cohabitation status in males and females. Mortality rates for both patients living alone and controls living alone, were about twice as high as for cohabiting patients and cohabiting controls respectively (Figure 12A). For patients, there was an interaction between gender and cohabitation status ( $p=0.039$ ) and men living alone had a mortality rate of 44% compared to 23% for women living alone, 14% for cohabiting men, and 22% for cohabiting women (log rank  $p<0.001$ , Fig 12B). A similar pattern, with the highest mortality rate for men living alone, was seen in controls (log rank  $p=0.007$ , Fig 12C).

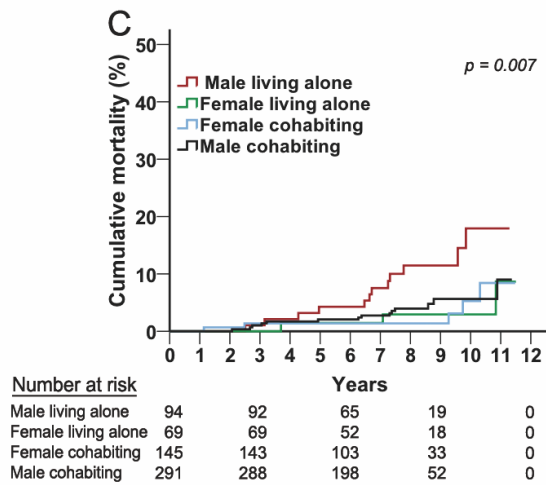
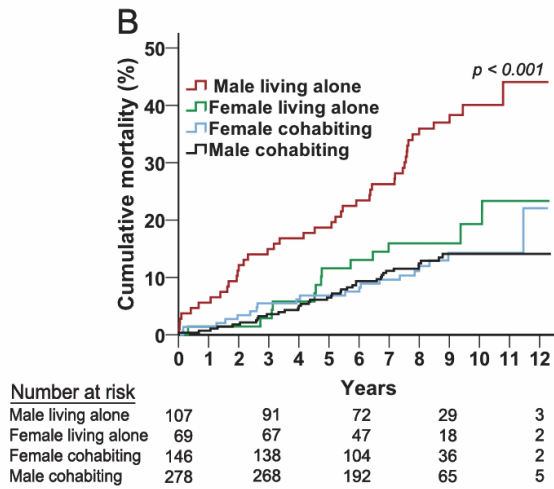
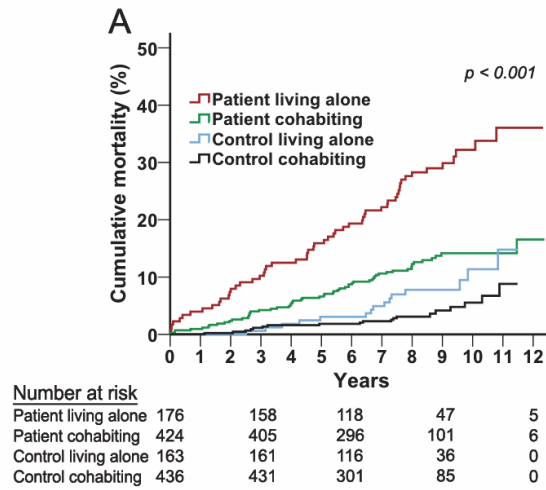
The multivariable adjusted HRs for all-cause mortality according to vascular risk factors, socioeconomic factors, stroke severity and stroke subtype are presented in Figure 13. Living alone showed a strong association with mortality whereas no associations were observed for the other socioeconomic factors. As expected increasing age showed a strong association. Diabetes and moderate stroke severity showed independent associations. With respect to stroke subtype, the subtypes LVD and CE stroke were associated with mortality.



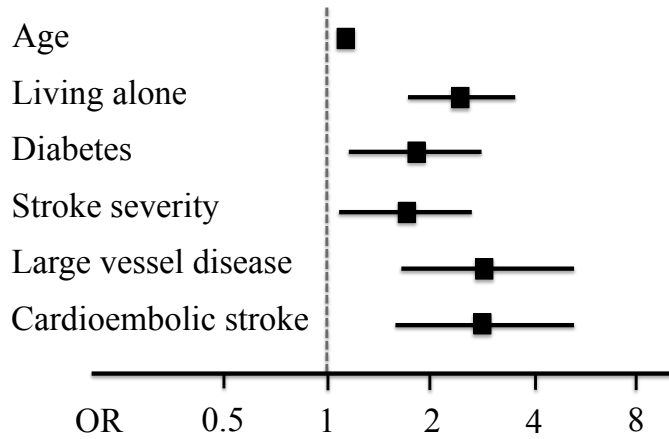
**Table 7.** Baseline characteristics for cases according to cohabitation status and gender.

	Cases n=600	Male cases cohabiting n=278	Male cases living alone n=107	Female cases cohabiting n=146	Female cases living alone n=69
Age, mean (SD) years	56 (10)	58 (9)	57 (10)	56 (12)	55 (12)
Male sex	385 (64)	-	-	-	-
Risk factors					
Hypertension	354 (60)	173 (62)	65 (64)	77 (53)	39 (57)
Diabetes	114 (19)	59 (21)	19 (18)	22 (15)	14 (20)
Hyperlipidemia	413 (76)	196 (76)	72 (79)	97 (72)	48 (79)
Smoking	233 (39)	85 (31)	52 (49)***	56 (39)	40 (58)†
Socioeconomic and life-style factors					
Occupation, lower education	364 (63)	143 (53)	73 (73)***	99 (71)	49 (74)
Sedentary leisure time	108 (19)	35 (14)	29 (30)***	25 (18)	19 (30)
Self-perceived psychological stress	126 (22)	51 (19)	14 (14)	41 (29)	20 (31)
Alcohol consumption >4 times a week	44 (8)	22 (8)	16 (17)*	5 (4)	1 (1)
Pre-stroke disability	233 (39)	9 (3)	11 (12)**	5 (4)	6 (9)
Comorbidities					
Personal history of stroke	114 (19)	58 (21)	19 (18)	27 (18)	10 (14)
Personal history of coronary disease	97 (17)	52 (19)	17 (19)	19 (14)	9 (14)
Stroke subtype					
SVD	124 (21)	49 (18)	28 (26)	32 (22)	15 (22)
LVD	73 (12)	37 (13)	17 (16)	15 (10)	4 (6)
CE stroke	98 (16)	50 (18)	16 (15)	22 (15)	10 (15)
Cryptogenic stroke	162 (27)	70 (25)	25 (23)	42 (29)	25 (36)
OD stroke	51 (9)	25 (9)	8 (7)	13 (9)	5 (7)
Undetermined stroke	92 (15)	47 (17)	13 (12)	22 (15)	10 (14)

Differences between groups were examined with the chi-square test or Fisher's exact test for proportions and Student's t-test for continuous variables. SVD indicates small vessel disease; LVD, large vessel disease; OD, other determined. \*p<0.05 versus males cohabiting, \*\*p<0.01 versus males cohabiting, \*\*\*p<0.001 versus males cohabiting. †p<0.01 versus females cohabiting.



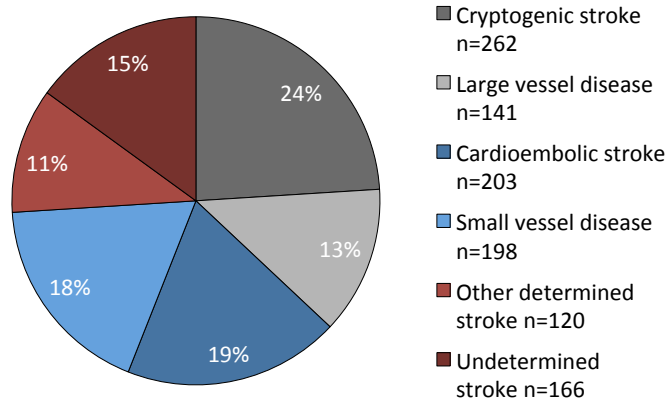
**Figure 12.** Survival curves according to cohabitation status for patients and controls (Panel A), for patients according to cohabitation status and gender (Panel B), for controls according to cohabitation status and gender (Panel C).



**Figure 13.** Adjusted hazard Ratios and 95% Cis for all-cause mortality.

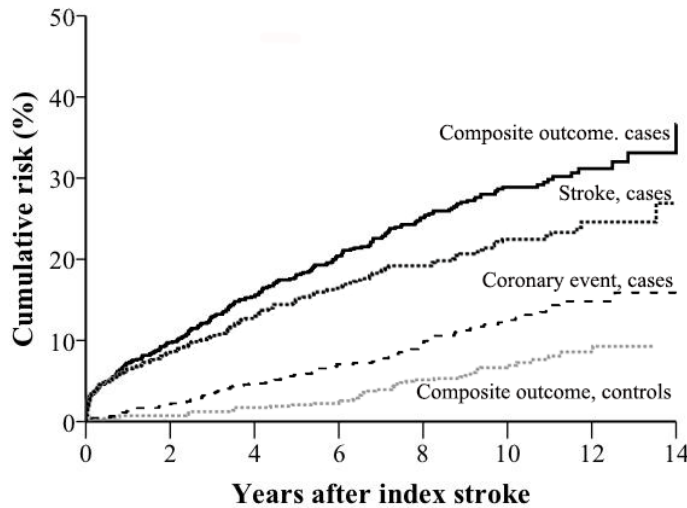
**High long-term risk of vascular events in patients with ischemic stroke before 70 years of age – results from the Sahlgrenska Academy Study on Ischemic Stroke (Paper IV)**

The median follow-up for the 1,090 patients was 6.3 years (IQR 2.8-10.3) and for the 600 controls 10.2 years (IQR 9.7-11.9); 7,161 and 6,313 person years for patients and controls respectively. The distribution of stroke subtypes is given in Figure 14.



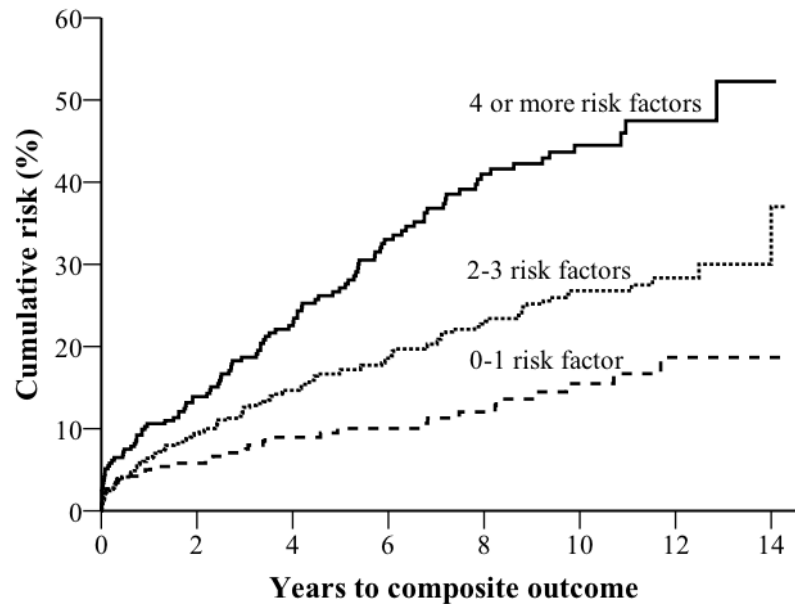
**Figure 14.** Distribution of ischemic stroke subtypes.

Figure 15 shows the cumulative risk for the composite outcome (i.e. stroke, coronary event and/or arterial thrombotic event), recurrent stroke and coronary events for patients and for the composite outcome for controls. A high proportion of the composite outcome consisted of recurrent stroke (cumulative risk 32% (95% CI, 28-36%) for the composite outcome and 24% (95% CI, 18-29%) for recurrent stroke after 12 years). The cumulative risk of the composite outcome for controls was more than three times lower than for patients, 9% (95% CI, 6-12%). During the follow-up period only 5% of controls had a coronary event and only 2% suffered a stroke.



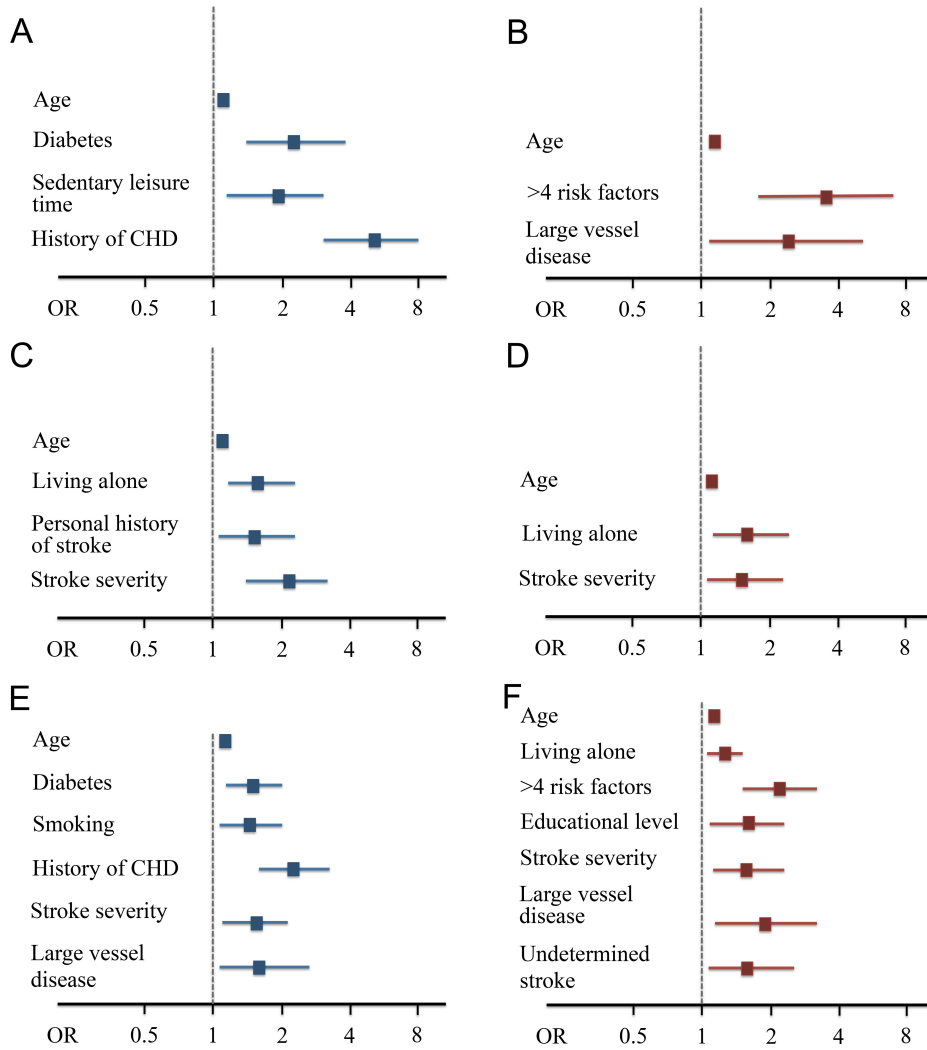
**Figure 15.** Cumulative risk of recurrent vascular events.

With respect to risk factor score (composed of risk factors considered as well-documented in the literature and described in the methods section),[72] 24% of the patients had 0-1 well-documented risk factors. Forty-nine percent had 2-3 risk factors and 27% had 4 or more risk factors. Figure 16 displays that the cumulative risk of the composite outcome was increased with increasing number of well-documented risk factors (cumulative risk 19% (95% CI, 12-26%) 0-1 risk factor, 30% (95% CI, 24-36%) 2-3 risk factors and 52% (95% CI, 41-64%) 4 risk factors). Only 6% had no risk factor, but there was no difference in composite outcome compared to those with 1 risk factor (data not shown).



**Figure 16.** Cumulative risk of the composite outcome stratified by number of well-documented risk factors (log rank  $p < 0.001$ ).

In univariate analyses, increasing age, hypertension, smoking, living alone, risk factor score number, low occupational class, history of stroke, history of CHD, moderate stroke severity, LVD, and undetermined stroke predicted recurrent stroke. In addition, diabetes, obesity, and CE stroke was associated with the composite outcome. Multivariable models for the composite outcome, fatal and non-fatal stroke and coronary events, including and not including number of well-documented risk factor as a score variable, are presented in Figure 17. Stroke subtype influenced the composite outcome in both models but only coronary events in the risk factor score model. Living alone predicted stroke in both models but only the composite outcome in the risk factor score model. Predictors of stroke and coronary events were different: living alone, personal history of stroke and moderate stroke severity were associated to stroke whereas diabetes, physical inactivity and a history of CHD were associated with coronary events.



**Figure 17.** Adjusted Hazard ratios and 95% CIs for coronary events (A, B), fatal and non-fatal stroke (C, D), and the composite outcome (E, F). Significant ( $p < 0.1$ ) variables in the univariate analysis and gender were entered into models A,C and E. A risk factor score number of well-documented risk factors (hypertension, diabetes, hyperlipidemia, obesity, smoking, sedentary leisure time, atrial fibrillation, history of stroke and history of coronary heart disease) was used in models B, D and F.

## DISCUSSION

The focus of this thesis has been to investigate long-term outcomes after ischemic stroke in young and middle-aged stroke sufferers. The recruitment of the large case-control study SAHLSIS has enabled us to follow not only patients but also controls over many years. We have, both for cases and controls, estimated rates of mortality, stroke and coronary events in long-term follow-up. Furthermore, great emphasis has been placed on classification of ischemic stroke subtypes and assessment of stroke severity, classical risk factors as well as socioeconomic and life-style factors. Taken together, this well-characterized cohort has enabled the investigation of predictors of vascular events after ischemic stroke. In the 7-year follow-up of SAHLSIS, great effort has been put on assessing hidden dysfunctions after ischemic stroke, as a high proportion of stroke survivors, even in the long-term perspective, suffer from neglect, depression and cognitive impairment. Therefore, as a first step in these analyses of long-term outcomes, paper II focuses on evaluating a screening instrument for cognitive dysfunction.

### **Risk of death, vascular events and recurrent stroke after ischemic stroke**

The five-year mortality rate for cases in SAHLSIS was comparable to studies including patients with ischemic stroke before 50 years of age. The risk of death was considerably higher for cases compared with controls throughout the follow-up period. This excess risk among the cases was due to more vascular deaths. There were also more deaths due to lung cancer among cases, probably explained by a higher proportion of smokers in this group compared to the control group.

We also assessed the risk of early stroke recurrence and found this risk to be quite high (5% after 3 months). Our findings of a relatively high early stroke recurrence rate, which declines and is more stable in subsequent years, is in line with results from previous studies.[25, 56] In contrast, the incidence of coronary events after ischemic stroke has been shown to be fairly constant over the years.[25, 35, 56] The same was true in our studies but we also observed a tendency towards a lower rate of coronary events the first year after ischemic stroke.

After a mean follow-up of 6 years almost a quarter of the cases suffered a

recurrent stroke whereas only every 8<sup>th</sup> patient suffered a coronary event during the follow-up period. The controls had considerably lower risks; 2% and 7% suffered a stroke and coronary event, respectively. As expected, the stroke recurrence rate was higher than in studies including only young stroke patients,[25, 35, 53] but lower than in stroke studies including all ages.[27, 48, 55]

### **Predictors of mortality and recurrent vascular events after ischemic stroke**

Consistent with findings in other long-term follow-up studies, both in young stroke and stroke in all ages, diabetes was a predictor of post-stroke mortality in our study. Diabetes was also a predictor of the composite outcome in paper IV. However, in contrast with some previous studies,[25, 48, 74, 75, 173] we did not identify diabetes as an independent predictor of recurrent stroke. One of the previous studies was in younger stroke and the association was with diabetes type 1. Most of the other studies were performed many years ago and it could thus be speculated that improved metabolic control among patients with diabetes in recent years has decreased their risk of vascular events.

Smoking is a shared risk factor for stroke, MIs, PADs, and certain types of cancer. This most likely explains the association with the composite outcome in paper IV. Therefore it is not surprising that smoking also has been associated with mortality in some previous studies.[27, 38]

An increasing amount of adults are living alone, and in our cohort the proportion was 29%. We showed that living alone was a strong predictor of both all-cause mortality and vascular mortality in long-term follow-up after ischemic stroke. The association was independent of vascular risk factors, occupational class, life-style factors, stroke severity and subtype. Living alone was also a predictor of mortality in controls. We also showed an association between living alone and with recurrent stroke in the extended cohort. These are interesting findings as only two studies have indicated that social support may be relevant for stroke outcomes and, to the best of our knowledge, the association between living alone and stroke recurrence has not been previously reported. A study from Manhattan[70] showed an association between social isolation and a combined outcome (i.e vascular events or death) in long-term follow-up after ischemic stroke and a small study from Norway[87] including patients <50 years, reported better survival among married patients. Moreover, an association



between a small social network and an increased risk of incident stroke was recently reported.[84] In contrast, to studies on stroke, there is more clear evidence for an association between low social support and increased mortality in patients with established CHD,[174] as well as between low social support and increased mortality in the general population.[82, 83]

Patients living alone in our study did not differ from cohabiting patients with regards to the proportion of patients having diabetes or hypertension, but differed regarding social- and life-style factors, i.e. they were more often smokers, more physically inactive in leisure-time, and more often had a lower occupational class. However, none of these factors had a significant influence on the mortality rate.

When stratified by gender, we found that the mortality rate was highest among male patients living alone. This is in line with results from studies on patients with MI,[90] and from health surveys of the general population.[175] Although the finding needs replication, the result indicate that men living alone are at a high risk of premature death after stroke despite current therapies for secondary preventions.

The mechanisms by which living alone may increase mortality after stroke is not clear but proposed explanations include delayed hospital arrival, [176], impaired health behaviour,[177] non-compliance to medication,[178] psychological distress,[175] and chronic inflammation.[179]

A limitation to our study with regard to living alone is that we have no data on psychosocial measures, such as functional social support or more detailed information on the structural support other than cohabitation status. However, an increasing amount of data supports that living alone may be used as a proxy for social isolation.[83, 86, 89, 180] Advantages with using cohabitation status as a marker of social isolation include that it is easily defined even in the acute stage of stroke without using complicated questionnaires. Secondly, we included a number of confounding factors, but have no data on depression. A recent review concludes that low social support/living alone and depression are independent risk factors for poor prognosis in cardiac disease.[181] However, the importance of post-stroke depression for mortality is not clear.[111]

We found that a history of CHD was predictive of both mortality and the composite outcome. As outlined in the introduction, cardiac disease (CHD and congestive heart failure) is a strong predictor of mortality in long-term follow-up

studies after ischemic stroke. Moreover, CHD and heart failure have also been associated with composite outcome in previous studies.[25, 27] It is of note that CHD influenced mortality in the first 4 years after stroke in our study, but not thereafter. Since CHD is a strong predictor of mortality it is a limitation that we did not include the variable in the 2-year follow-up study.

A personal history of stroke at baseline was not a predictor of mortality in our study. Most previous studies only included first-ever stroke, but in studies like ours that also included recurrent stroke a higher mortality was reported for patients with a history of stroke.[47] However, prior stroke was not a significant predictor in the only study on young stroke patients that included both first-ever and recurrent stroke.[42] One explanation for the divergent findings may be that history of stroke has a larger impact on mortality among elderly stroke subjects. A personal history of stroke in our study was also associated with recurrent stroke, but again only one previous study included both first-ever and recurrent stroke, making comparisons difficult.

Severe index stroke is a well-known and strong predictor of short-term mortality after ischemic stroke.[182] Most studies conducted in recent years have included stroke severity as a baseline variable, and have also identified increasing stroke severity at index stroke as a predictor of long-term mortality. The impact of index stroke severity is thought to decrease with time in long-term follow-up.[68] Nevertheless, in our studies stroke severity was an important predictor of mortality both in 2-year and in very long-term follow-up. Moreover we found that it also influenced stroke recurrence, which has not been demonstrated previously. However, with respect to stroke recurrence, stroke severity was a time-dependent variable, and there was no influence 10 years after index stroke.

Increasing evidence suggests that stroke subtype is independently associated with mortality after ischemic stroke, even in the long-time perspective. This seems to be true across all ages and LVD and CE stroke are the subtypes most commonly reported to be associated with increased risk. The results in paper IV support these findings. Although Putaala et al identified LVD as an independent predictor of stroke recurrence,[25] the influence of stroke subtype on the long-term recurrence rate after ischemic stroke is a matter of debate. In our studies, we identified LVD as a predictor of the composite outcome in paper I, and IV, but stroke subtype was not a predictor of recurrent stroke or coronary events. The interpretation could be that the influence of stroke subtype differs by age or that the lack of association between LVD and stroke recurrence in the present study was due to lack of power. An alternative explanation could be that the

LVD patients have generalized atherosclerotic disease and thus have an increased risk mainly of mortality and thus also of the composite outcome. When it comes to stroke recurrence, all stroke subtypes can have a common pathway, e.g. a prothrombotic state, leading to an increased risk of stroke, and thus all subtypes may have similar risk of stroke recurrence.

In study IV, a score comprising the number of well-documented risk factors was used. This score has previously been shown to be prognostically relevant for the composite outcome in patients aged <50 years,[25] but not for the outcome recurrent stroke, and this was also true in our study. Moreover, we found a risk factor score of 4 to predict coronary events in line with findings from Putaala et al.[183] In the multivariable models including the risk factor score, the less-well documented risk factors were retained, indicating the importance of assessing not only classical risk factors when estimating stroke prognosis. To conclude, an interesting finding was that the risk factor score independently predicted coronary events but not recurrent stroke. One interpretation may be that stroke is a more complex and heterogeneous disease compared to cardiovascular disease and that the identification of novel predictors may help in improving secondary prevention measures after ischemic stroke.

### **Predictors of coronary events after ischemic stroke**

The rationale beyond the hypothesis that different stroke subtypes bear different risk of recurrent vascular events is that the subtypes have highly diverse etiologies. LVD is caused by atherosclerosis and most CHD cases are also attributable to large artery atherosclerosis, thus it seems likely that LVD has higher risk of subsequent coronary events compared with other subtypes. However, in the model including all relevant variables no association between stroke subtype and coronary events was detected. Interestingly, as mentioned above, in the model including the risk factor score, LVD was moderately but significantly associated with future coronary events, thus supporting this hypothesis. Furthermore, in a study from Greece, which also addressed this question, SVD and CE stroke had less coronary events compared with LVD.

In line with the findings in our study, other long-term studies after stroke/ischemic stroke have identified established cardiac disease as a major predictor of coronary events.[27, 57, 120] Furthermore, in concordance with our results, diabetes was risk factor for MI after stroke in a study from

Umeå[120] and high levels of glucose at admission was a predictor in the study from Greece.[27]

Interestingly, being physically inactive in leisure time before the index stroke, showed an independent association with coronary events. This has not been reported before, but high leisure time physical activity was associated with reduced risk of incident MI in the INTERHEART study.[184]

To conclude, mortality due to cardiac causes was slightly more common than mortality due to stroke. Thus, patients having suffered an ischemic stroke, clearly has a high risk of subsequent coronary events, especially if taking into account fatal coronary events. However, in our view, a personal history of CHD is the most important factor in increasing the risk of coronary events, whereas it is still not clear whether the risk is higher with certain stroke subtypes.

### **Predictors of functional outcome after ischemic stroke**

Studies on short-term functional outcome including neurological deficit at discharge, almost consistently show that initial stroke severity is an independent predictor of functional outcome.[60, 185-187] In short-term follow-up after ischemic stroke, favourable short-term functional outcome has been reported for SVD, whereas CE stroke has been associated with poor short-term functional outcome.[24, 173, 188, 189] However, these studies did not adjust for important vascular risk factors and stroke severity. A recent study from Finland, including adjustment for stroke severity, reported an independent association with SVD and good functional outcome 3 months after stroke.[190]

To our knowledge the influence of stroke subtype on long-term functional outcome has not been investigated. In 2-year follow-up, we found an association between stroke subtype and functional outcome that was not retained after entering stroke severity in the model. The reason could of course be that the effect of stroke subtype on functional outcome is mainly mediated through stroke severity, which differs by stroke subtype.[19] Recent long-term follow-up studies have also showed strong associations between stroke severity and poor functional outcome.[62, 121] As expected, recurrent stroke has been shown to influence functional outcome in long-term follow up-studies[62, 121] and it is a limitation that we did not include the variable in our analysis.

## **BNIS as a screening instrument after ischemic stroke**

In paper II we evaluated the BNIS as a screening instrument 7 years after ischemic stroke. The BNIS is currently used in clinical practice, both at the Neurorehabilitation Unit and by neuropsychologists at the Department of Neurology in Gothenburg. We distributed the BNIS and the MMSE to 295 stroke survivors. A large proportion was able to complete both tests, but 5% did not pass the pre-screen items, mainly due to severe aphasia. We found good psychometric qualities for the BNIS: the BNIS total score was normally distributed, no subscale except orientation had ceiling effects and almost all subscales differentiated well between levels of cognitive ability. This contrasts to the results from the screening with the MMSE where we found pronounced ceiling effects both with the total and the subscales scores and the scores on most of the different subscales had poor spreading.

A recent study confirmed the BNIS as promising tool for detecting cognitive dysfunction after stroke. In this study of stroke patients with good functional outcome the BNIS results showed a moderate to strong correlations with corresponding neuropsychological tests used in the study.[191] In our study, the subscales evaluating attention/concentration, memory, visuospatial problem-solving and awareness were most affected.

Few studies have assessed cognitive dysfunction among young and/or middle-aged patients at long-term follow-up, but studies have shown that even stroke patients with good functional outcome with respect to neurological deficits may have significant cognitive impairments.[192, 193] Our results, using the BNIS, indicate a very high proportion with possible cognitive dysfunction (89%) many years after stroke in young and middle-aged survivors. However, it should be noted that although the standard cutoff level of <47 was reported to be optimal in stroke patients below 55 years in a recent small study (n=54), comparing the BNIS to a formal neuropsychological examination, the specificity was low (39%). In stroke patients >55 years, lowering the cutoff to <41 yielded high sensitivity (92%) and specificity (85%).[191] Similar findings, with cognitive dysfunction among >90% of patients evaluated by a neuropsychological test battery, was reported in the subacute phase after stroke in a young stroke cohort.[194]

Screening instruments for cognitive dysfunction, including the MMSE, are influenced by age, education and depression[172] In our study, the BNIS total score was associated with age, educational level, having had multiple stroke and

depressive symptoms, but not by gender. Future research on correcting the cutoff score for educational level may improve the specificity, as there are some difficult items in the BNIS (i.e. the number/symbol test in the memory item and the pattern recognition in the visual problem-solving item).

## CONCLUSION TO GIVEN AIMS

- In patients with ischemic stroke before 70 years of age, the stroke subtype LVD predicts recurrent vascular events and/or death 2 years after index stroke independently of cardiovascular risk factors and stroke severity. For functional outcome, stroke severity at index stroke is the most important independent predictor, whereas stroke subtype was not retained in the multivariable analysis.
- The BNIS is a useful screening instrument for cognitive dysfunction in young and middle-aged stroke survivors. Further validation against neuropsychological testing is needed.
- Living alone is a predictor of long-term mortality after ischemic stroke in young and middle-aged stroke sufferers. The association is independent of vascular risk factors, socioeconomic factors, stroke severity and stroke subtype. There is an interaction between living status and gender, with highest mortality is in male patients living alone.
- In patients with ischemic stroke before the age of 70 years, the risk of vascular events is high throughout a 12-year period after the index stroke. The rate of recurrent stroke is much higher than the rate of coronary events Independent predictors of vascular events are increasing age, diabetes, smoking, history of CHD, stroke severity, and LVD underlying the index stroke.

## FUTURE PERSPECTIVES

Within SAHLSIS an extensive 7-year follow-up is performed, which for instance includes neuropsychological testing, MRI of the brain to identify and quantify white matter disease (WMD) as well as assessments of different functional outcomes, daily activities, participation, depressive symptoms, and fatigue. Thus, further studies of this cohort will continue to provide a wealth of exciting data on long-term outcomes after ischemic stroke in working age.

Evaluating MRI at baseline and at 7-year follow-up, with quantification of progression of WMD, is an ongoing project within SAHLSIS and will give us opportunities to seek associations with the BNIS and its subscales. Another interesting project would be to study associations between 7-year functional outcome and WMD. Furthermore, although the BNIS seems promising as a screening instrument for cognitive dysfunction, studies with neuropsychological comparisons to determine cutoffs in relation to age and educational level are needed. In addition, future studies on biomarkers as potential predictors of poor outcomes may lead us towards a better understanding of pathways influencing the prognosis following stroke.

With regards to our finding of a poor prognosis after ischemic stroke among patients living alone, the question whether this association is casual or not remains to be solved. However, our results indicate that clinicians should consider living alone as a modifiable risk factor. A first step is of course to seek replication of the findings, but then another important step forward would be interventional rehabilitation studies. These should be targeted to give psychological support and to improve the health behaviours that we know are poorer in patients living alone, e.g. adherence to treatment recommendations, physical activity, diet and smoking. Furthermore, some evidence support that chronic inflammation could be a mediator between social isolation and mortality, in particular among men, thus investigating biomarkers in this context in our cohort would be of interest.

A long-term future scenario, which our ongoing and future studies may contribute to, would be individualized patient tailored secondary preventive measures starting already in the acute stroke care setting and continuing in long term follow-up.



## POPULÄRVETENSKAPLIG SAMMANFATTNING

Stroke är en av de vanligaste orsakerna till död och handikapp i världen och i Sverige. De flesta som drabbas är äldre, men stroke kan drabba personer i alla åldrar och mer än en tredjedel av de som drabbas är under 70 år. De senaste åren har flera studier visat att insjuknandena i stroke ökar i den yngre och medelålders befolkningen i västvärlden. Följderna av stroke i ett långtidsperspektiv är omfattande, det är vanligt med kvarvarande funktionsnedsättning och nedsatt kognition\*. Dessutom finns risk att drabbas av ny stroke, hjärtinfarkt eller till och med död.

Stroke kan indelas i hjärninfarkt (ischemisk stroke) och hjärnblödning (hemorrhagisk stroke). I denna avhandling studeras enbart hjärninfarkt som är vanligast förekommande och utgör 85% av all stroke. Hjärninfarkt orsakas ofta av att en blodpropp hindrar blodtillförseln till en del av hjärnan, vilket leder till brist på syre och näringsämnen och slutligen vävnadsdöd och hjärnskada. Ofta indelas hjärninfarkt i olika subtyper beroende på den bakomliggande orsaken och man har också visat att subtyperna har olika prognos. De fyra vanligaste orsakerna till hjärninfarkt är: storkärlssjuka som innebär åderförkalkning i ett större blodkärl till hjärnan, småkärlssjuka som är orsakad av proppbildning i ett litet kärl i hjärnan, kardioembolisk stroke där en blodpropp bildas lokalt i hjärtat och transporteras via blodkärl till hjärnan och kryptogen stroke som innebär att man trots extensiv utredning inte har kunnat hitta någon orsak till stroke.

Det som inte är så väl studerat är hur olika livsstilsfaktorer och socioekonomiska faktorer liksom subtyp av stroke kan påverka risken för återinsjuknande och död. Tidigare studier har också ofta inriktat sig på att studera stroke orsakad av hjärninfarkt och hjärnblödning som en entitet, trots att det finns skäl att anta att prognostiska markörer skiljer sig mellan dessa två typer av stroke. Vidare finns det få studier med långtidsuppföljning som har inkluderat så många patienter att det går att hitta prognosmarkörer.

*\*Kognition är en samlingsterm för de mentala processer, normalt viljestyrda, som handlar om förmåga att lära, tänka och bearbeta information i hjärnan.*

Syftet med den aktuella avhandlingen var därför att efter hjärninfarkt uppskatta riskerna för återinsjuknande, hjärtinfarkt och död och jämföra dessa med motsvarande risker hos friska kontroller. Vidare att identifiera prognostiska markörer för nya vaskulära händelser, funktionsnedsättning och död med särskilt fokus på subtyper och livsstilsfaktorer.

Alla studier baseras på fall-kontroll studien "the Sahlgrenska Academy Study on Ischemic Stroke" (SAHLSIS) som utgörs av 1,090 patienter som drabbats av hjärninfarkt före 70 års ålder och 600 friska kontroller. Patienterna och kontrollerna har utretts noggrant med avseende på bland annat andra sjukdomar, livsstilsfaktorer och socioekonomiska faktorer. Två år efter sin stroke intervjuades patienterna per telefon och efter 7 år har de utfört det kognitiva screeningtestet "the Barrow Neurological Institute Screen for Higher Cerebral Functions" (BNIS). Vidare har vi samlat in fakta om återinsjuknanden och död via dödsorsaksregistret, patientregistret och patientjournaler.

I vår 2-års uppföljning fann vi att ju högre handikappgrad som stroke orsakade akut desto högre var risken för både ny stroke/hjärninfarkt och död och för att vara beroende av andra i dagliga aktiviteter. Vidare ökade risken för ny stroke/hjärninfarkt och död om orsaken till stroke var storkärlssjuka.

Resultaten från 12-års uppföljning av deltagarna i SAHLSIS visar att strokepatienterna under uppföljningsperioden, hade 10 gånger högre risk att drabbas av stroke jämfört med de friska kontrollpersonerna, medan risken att insjukna i hjärtinfarkt var dubbelt så hög hos patienterna jämfört med kontrollerna. Hög ålder ökade som förväntat risken att dö och att drabbas av ny stroke eller hjärtinfarkt.

Vi fann att livsstilsfaktorer hade betydelse för prognosen. Risken att dö och att drabbas av ny stroke var ökad om man bodde ensam utan partner vid insjuknandet. Den allra högsta risken hade ensamboende män: risken att dö var 44% för ensamboende män, att jämföra med risken för sammanboende män som var 14%. Vidare hade patienter som var fysiskt inaktiva före insjuknandet högre risk att få hjärtinfarkt under uppföljningsperioden.

Andra mer klassiska riskfaktorer som var associerade med död var diabetessjukdom, den akuta handikappgraden som stroke orsakade och om orsaken till stroke var storkärlssjuka eller kardioembolisk. Förutom att ökande ålder hade negativ inverkan på prognos, så skiljde sig riskfaktorerna åt med avseende på risk att drabbas av ny stroke eller hjärtinfarkt. Att vara

ensamboende, att tidigare haft stroke och om stroke orsakade en hög grad av handikapp vid insjuknandet var av betydelse för nytt strokeinsjuknande, medan diabetes, fysisk inaktivitet och att ha kranskärslsjukdom ökade risken för drabbas av hjärtinfarkt i långtidsuppföljningen.

Det kognitiva screeninginstrumentet BNIS fungerade väl och vi fann att en hög andel av patienterna (89)% har möjlig nedsatt kognition 7 år efter strokeinsjuknandet.

Sammanfattningsvis, så har patienter som insjuknar med hjärninfarkt före 70 års ålder en hög risk att dö eller drabbas av ny stroke eller hjärtinfarkt även många år efter insjuknandet. Klassiska riskfaktorer som diabetes, rökning eller etablerad kranskärslsjukdom har betydelse för prognos, men även den akuta graden av handikapp som stroke orsakar vid insjuknandet och strokesubtyp. En ny kunskap från våra studier är att ensamboende patienter har ökad risk för död och ny stroke. Våra studier belyser vikten av fortsatt och intensiv behandling av riskfaktorer hos strokepatienter många år efter insjuknandet.

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