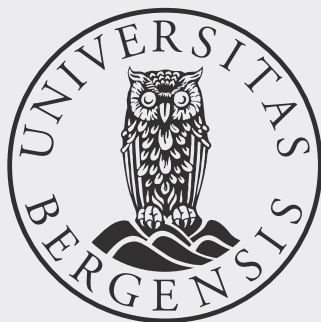




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Risk factors influencing long-term survival and nursing home placement in stroke survivors • Sara Maria Mathisen

Risk factors influencing long-term survival and nursing home placement in stroke survivors and patients with carotid stenosis

Sara Maria Mathisen

Thesis for the degree of Philosophiae Doctor (PhD)

University of Bergen, Norway

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Thesis for the degree of philosophiae doctor (PhD)
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Abbreviations

ACSRS	Asymptomatic Carotid Stenosis Risk Stratification study
ADL	activities of daily living
AF	atrial fibrillation
AHA	American Heart Association
ANOVA	one-way analysis of variance
APTT	activated partial thromboplastin time
BI	Barthel Index
BMI	Body Mass Index
BP	blood pressure
CAS	carotid artery stenting
CCA	common carotid artery
CEA	carotid endarterectomy
CT	computer tomography
CTP	computer tomography perfusion
CTA	computer tomography angiography
CVDs	cardiovascular diseases
DALY	disability-adjusted life-years
DM	diabetes mellitus
DOAC	direct oral anticoagulants

ECG	electrocardiogram
ECA	external carotid artery
ECST	European Carotid Surgery Trial
EDV	end-diastolic velocity
ESD	early supported discharge
EVT	endovascular treatment
FHS	Framingham Health Study
FLAIR	fluid-attenuated inversion recovery
GFR	glomerular filtration ratio
HCY	homocystein
HDL	high-density lipoprotein
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HR	hazard ratio
ICA	internal carotid artery
ICH	intracerebral hemorrhage
ICD-10	International classification of diseases, 10 th revision
IDL	intermediate density lipoprotein
INR	international normalized ratio
IVT	intravenous thrombolysis
LAA	left atrial appendage

LDL	low-density lipoprotein
MI	myocardial infarction
MRI	magnetic resonance imaging
MRP	magnetic resonance perfusion
MRA	magnetic resonance angiography
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NH	nursing home
NHP	nursing home placement
NIHSS	National Institutes of Health Stroke Scale
OR	odds ratio
PSV	peak systolic velocity
PSVR	peak systolic velocity ratio
RR	relative risk
SAH	subarachnoidal hemorrhage
SBP	systolic blood pressure
SSS	Scandinavian Stroke Scale
SUS	Stavanger University Hospital
TIA	transient ischemic attack
rt-PA	recombinant tissue plasminogen activator
VLDL	very low-density lipoprotein

WHO World Health Organization

Abstract

Risk factors influencing long-term survival and nursing home placement in stroke survivors and patients with carotid stenosis

Stroke is one of the leading causes of mortality and morbidity worldwide and one of the most devastating of all neurological conditions. Due to the many advances that have been made in terms of prevention and mortality in cardiovascular diseases, the mortality from stroke has declined steadily and more patients survive their strokes. Short-term mortality is intensely studied. Knowledge of long-term mortality and its clinical predictors offers the opportunity to better control the risk factors in the follow-up after a stroke.

We have investigated long-term survival for up to 12.8 years and causes of death in 230 patients with $\geq 40\%$ ICA-stenosis that is a known risk factor for stroke regarding statin treatment. The results indicate that use of statins seems to increase long-term survival in patients with established carotid artery stenosis significantly compared to patients not using statins.

We also examined the long-term mortality for up to 16.4 years in 1137 patients with acute stroke and compared it to a matched, stroke-free control group. We identified risk factors present at index stroke that might predict long-term mortality. The results indicate that stroke patients surviving the first year after stroke have a markedly increased but stable mortality rate during long-term follow-up compared to stroke free controls. Changes in creatinine, homocysteine and glucose could be addressed more aggressively as a standard routine after acute stroke.

The 452 patients belonging to the municipality of Stavanger were followed for up to 15.4 years regarding nursing home placement (NHP). Almost 90% of the stroke patients could initially be discharged to their homes but they needed earlier and more often NHP in the long run than the stroke-free controls, but they did not stay longer.

List of publications

Wörlund SM, Kurz MW, Hegland O, Brønnick K, Munk PS, Larsen JP. Treatment with statins improves long-term survival in individuals with carotid artery stenosis. *Int J Cardiol.* 2013 Sep 20;168(1):624-6

Mathisen SM, Dalen I, Larsen JP, Kurz M. Long-Term Mortality and Its Risk Factors in Stroke Survivors. *J Stroke Cerebrovasc Dis.* 2016 Mar;25(3):635-41

Mathisen SM, Larsen JP, Kurz MW. The prognosis of stroke survivors primarily discharged to their homes. *Acta Neurol Scand.* 2017 Jan 27. doi: 10.1111/ane.12731.

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1. Introduction

1.1 Brief history and definition of acute cerebral stroke

The word “stroke” was first introduced into medicine in 1689 by William Cole in “A Physico-Medical Essay Concerning the late frequencies of Apoplexies” (1). Before this, very acute non traumatic brain injury was described as “apoplexy” – a concept established by Hippocrates circa 400 BC (2).

The World Health Organization (WHO) defines stroke as: “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24h or longer or leading to death, with no apparent cause other than of vascular origin” (3, 4). The pathological background is either ischemic or hemorrhagic disturbance of the cerebral blood circulation.

1.2 Stroke subtypes

1.2.1 Ischemic stroke (infarction)

An expert consensus group convened by American Heart Association/American Stroke Association (AHA) modified the definition of an ischemic stroke in 2013 to “An episode of neurological dysfunction caused by focal cerebral, spinal or retinal infarction” (5).

Cerebral infarction results from the obstruction of cerebral and/or cervical arteries with hypoperfusion and ischemia in the territory of the occluded artery. The obstruction can be due to thrombosis of a pre-existent stenosis or due to embolism from a more distal artery wall lesion. Arteriosclerotic stenosis, dissection and vasculitis cause changes in artery walls that can contribute to the occlusion. An embolism is a blockage-causing piece of material that is delivered by the bloodstream

and blocks an intracerebral artery. The most common origin is in the heart, the aorta or the carotid or vertebral arteries. About 85% of all strokes are ischemic.

1.2.2 Hemorrhagic stroke

The definition of a hemorrhagic stroke (ICH) was redefined by the AHA in 2013: “Rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma” (5). Spontaneous intracerebral hemorrhages are mainly due to arteriolar hypertensive disease. Coagulation disorders, vascular malformations within the brain and diet (such as high alcohol consumption, drug abuse and low cholesterol concentration) are more rare causes. Cortical amyloid angiopathy, the deposition of β -amyloid in the media and adventitia of small and mid-sized arteries, is a cause of cortical hemorrhages especially occurring in elderly patients leading to multiple spontaneous smaller bleedings. These can be “silent” without a history of acute neurological dysfunction attributable to the lesion. Hemorrhagic strokes are less common than ischemic stroke but they are associated with higher mortality and morbidity than ischemic strokes (6). About 15% of all strokes are hemorrhagic.

1.2.3 Subarachnoidal bleeding

This subgroup of hemorrhagic stroke (up to 7%) (7) is mainly due to spontaneous rupture of aneurysms at the bifurcations of large arteries at the inferior surface of the brain. A stroke caused by subarachnoidal hemorrhage (SAH) is defined as “rapidly developing signs of neurological dysfunction and/or headache because of bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma” (5). Often, they do not cause direct injury to the brain and are excluded from stroke-studies, but beside acute and intense headache the symptoms may be in accordance with the stroke

definitions. The mortality is high (45%) (8) and the survivors of a subarachnoidal bleeding often have a high rate of disability (9, 10).

1.2.4 Transient ischemic attack (TIA)

The Stroke Council of the American Heart Association (AHA) defined in 2009 a TIA as “a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction” (11). A TIA is a temporary blockage of blood flow to the brain and associated with increased likelihood of a coming stroke: Thus, a TIA is often labeled as a “warning stroke” and offers an opportunity to initiate prophylactic treatment (12, 13). Former definitions were time based and presumed that the neurological symptoms dissolved within 24 hours. However, advances in radiology as high-resolution CT and especially diffusion-weighted MRI have shown that many short-lasting ischemic episodes are associated with infarction, making the time-limits inconsistent and outdated. Approximately 15% of all strokes are preceded by a TIA (14, 15), and the risk of a stroke following a TIA is up to 17% after three months (16).

1.3 Epidemiology

Stroke researchers in Norway calculated in 2007 that there would be approximately 11.000 first-ever strokes and 3500 recurrent ones per year for the next years according to incidence numbers (17) and population statistics (18). According to the national Stroke Register, 8538 strokes were reported in 2015 but the data here only cover 84% of the strokes registered in the national Norwegian patient register (19). But, as in the rest of the world the incidence is expected to increase with up to 50% until 2030 due to the ageing population (20, 21). The burden of stroke due to illness, early death and disability is set to double worldwide within the next 15 years (22). In Norway the median age at stroke is 75 years (mean age 77.5 years for women and

71.9 years for men) (19), in the UK, the mean age at first stroke for men is 74 years and for women 80 years (23).

The lifetime risk for suffering a stroke remains relatively constant until age 75, approximating 1 in 5 for women and 1 in 6 for men (24). In 2010, there were almost 17 million first-time strokes worldwide (22). The age-standardized prevalence rate of stroke in developed countries for people aged ≥ 65 years ranges from 46 to 72 per 1000 population (7). In the younger age groups up to 75 years, more stroke patients are male (25) but in total more females suffer a stroke and accordingly their lifetime risk and direct mortality is higher (26). Overall stroke prevalence in the United States is 2,7% (27).

When considered separately from other cardiovascular diseases (CVDs), stroke is number two among causes of death, behind diseases of the heart but in front of chronic lower respiratory and chronic obstructive disease, cancer, and unintentional injuries/accidents in the world (28). In the low-income countries, it is number three after lower respiratory diseases and diarrheal diseases (28). In the USA stroke has fallen to fourth most common cause of death, overtaken by lower respiratory diseases (29). Stroke deaths accounted for 11.8% of total deaths worldwide in 2013 (30). From 1970 to 2008 there has been a 42% decrease in stroke incidence in high-income countries and more than a 100% increase in low to middle income countries, where the majority of global stroke burden now resides (31, 32).

The decline in stroke rates in the developed countries occurred over a period of significant increase in the use of medications that attenuate stroke risk: Statin use increased from 4% in 1992 to 41% in 2008 and antihypertensive drug use increased from 53% to 74% in the same time (33, 34). Cost-effective medications such as aspirin, statins, and blood pressure lowering agents still remain unaffordable in large parts of the world.

1.4 Etiology and pathophysiology of acute cerebral stroke

The etiology of a stroke is brain tissue hypoperfusion caused by either ischemia or hemorrhage, and proportions range from 67% to 81% for ischemic stroke, 7% to 20% for primary intracerebral hemorrhage and 1% to 7% for subarachnoid hemorrhage while 2% to 15% remain undetermined (31). Other causes for cerebral hypoperfusion are sinus thrombosis (impaired cerebral venous drainage), vascular malformations, vasculitis, hematologic disorders and systemic hypoperfusion (septic shock, cardiac arrest i.a.).

Stroke is a very heterogenous and multifactorial disease. In addition to other, conventional risk factors genetic factors may contribute to a significant proportion of stroke. The genetics can be polygenic, monogenic or multifactorial (35, 36) but single-gene mutations count for approximately only 1% of ischemic strokes. However, there are certain known gene mutations leading to increased risk for strokes. Examples are mutations in the NOTCH3-receptor leading to CADASIL and mutations in α -galactosidase A leading to Fabry disease (35).

During local or systemic hypoperfusion insufficiency of blood supply leads to shortage of oxygen and glucose to the brain tissue. This leads to ischemic, necrotic cell death and is characterized by swelling (oncosis) of the mitochondrions, cytoplasm and nucleus and cytoplasm vacuolization (37). Apoptotic death will also occur, induced by several different stimuli as nitric oxide production, free radical formation and increased intracellular calcium which all prevail during ischemia (38). Specific brain regions and distinct neuronal populations appear to be more commonly affected due to higher metabolic rates or location in vascular border zones which make them more vulnerable (39). The hippocampus, the cerebellum, the basal ganglia and the watershed area belong to these regions.

1.5 Clinical manifestations

A stroke manifests with sudden loss of function corresponding to the location of the underlying vascular disturbance. Most often acute motor and sensory deficits like paresis and numbness can be seen. Language disturbances as aphasia or dysarthria are also common and a stroke might present with sudden vertigo, headache, balance problems, visual field affections or a combination of the aforementioned symptoms.

1.6 Clinical examination

When a patient arrives at the hospital with an acute stroke, a clinical examination is performed to validate the neurologic deficits and to confirm the clinical stroke diagnosis. Radiologic neuroimaging is done primarily to exclude contraindications to acute thrombolytic treatment (see 1.7.1 Radiologic neuroimaging). The clinical examination is standardized and systematic, including systematic assessment tools that provide a quantitative measure of stroke-related neurologic deficit. Today, the National Institutes of Health Stroke Scale (NIHSS) is most commonly used. The Scandinavian Stroke Scale (SSS) is an alternative assessment tool that was used frequently some years ago. It was the standard tool used at the Stavanger University Hospital (SUS) before 2009.

1.6.1 SSS

The Scandinavian Stroke Study Group performed in 1985 a multicenter study in Scandinavia to evaluate the effect of early hemodilution treatment in ischemic stroke patients. They did not find an available scoring system suitable for the study, and therefore constructed a scoring scale (Scandinavian Stroke Scale, SSS) adjusted to this study to be used by non-neurologists in general medical wards (40). This scale was routinely used at SUS before introducing the NIHSS scale in 2009. The SSS is

designed to give a score based on level of consciousness, eye movements, motoric function in the arm, hand, leg on the affected side and gait as well as orientation, speech and facial paralysis (Table 1.). The scale has good to excellent reliability and has been as well validated for retrospective use (41).

Scandinavian Stroke Scale (SSS)		
	Stroke scale item	Score values
1	Level of consciousness	0 - 6
2	Eye movements	0 - 4
3	Arm, motor power*	0 - 6
4	Hand, motor power*	0 - 6
5	Leg, motor power*	0 - 6
6	Level of consciousness Questions	0 - 6
7	Speech	0 - 10
8	Facial palsy	0 - 2
9	Walking	0 - 12
	* Motor power is only assessed on the affected side	Max. 58

Table 1. Scandinavian Stroke Scale (SSS)

1.6.2 NIHSS

The NIHSS is a systematic assessment tool that provides a quantitative measure of stroke-related neurologic deficit (42). The scale is widely used as a clinical assessment tool to evaluate the deficiency in stroke patients, to determine appropriate treatment, and to predict patient outcome. The NIHSS is a 15-item neurologic examination stroke scale used to evaluate the effect of acute cerebral infarction on the levels of consciousness, language, neglect, visual-field loss, extraocular movement, motor strength, ataxia, dysarthria, and sensory loss (Table 2.). NIHSS can be interconverted with SSS by using the following equation: $SSS = 50 - 2 \times NIHSS$ (Ali 07) or $SSS = 50.37 - 1.63 \times NIHSS$ (43) and has been shown to be equally good in

identifying 3 month outcome (44). The NIHSS is validated as an accurate tool for assessing stroke severity and is perceived as an excellent predictor for patient outcome with smaller NIHSS indicating smaller stroke lesion volume (45, 46).

	Stroke scale item	Score values
1a	Level of consciousness (LOC)	0 - 3
1b	Level of consciousness Questions	0 - 2
1c	Level of consciousness Commands	0 - 2
2	Horizontal eye movement	0 - 2
3	Visual field test	0 - 3
4	Facial palsy	0 - 3
5a	Motor left arm	0 - 4
5b	Motor right arm	0 - 4
6a	Motor left leg	0 - 4
6b	Motor right leg	0 - 4
7	Limb ataxia	0 - 2
8	Sensory	0 - 2
9	Language	0 - 3
10	Dysarthria	0 - 2
11	Neglect	0 - 2

Table 2. National Institutes of Health Stroke Scale (NIHSS)

1.6.3 Barthel Index

The Barthel scale or Barthel ADL index (BI) is a widely used ordinal scale used to measure functional disability by ranking performance in activities of daily living (ADL). Each performance item is rated on this scale with a given number of points assigned to each level or ranking, maximum 100 points (47). It uses ten variables describing ADL and mobility (feeding, bathing, grooming, dressing, bowel control, bladder control, toileting, chair transfer, ambulation and stair climbing).

Today, the Barthel ADL-index used has the same parameters but the maximum score is 20 (Table 3.).

	Activity	Score	Score
1	Feeding	0 - 5 - 10	0 - 1 - 2
2	Bathing	0 - 5	0 - 1
3	Grooming	0 - 5	0 - 1
4	Dressing	0 - 5 - 10	0 - 1 - 2
5	Bowel control	0 - 5 - 10	0 - 1 - 2
6	Bladder control	0 - 5 - 10	0 - 1 - 2
7	Toileting	0 - 5 - 10	0 - 1 - 2
8	Chair transfer	0 - 5 - 10 - 15	0 - 1 - 2 - 3
9	Ambulation	0 - 5 - 10 - 15	0 - 1 - 2 - 3
10	Stair climbing	0 - 5 - 10	0 - 1 - 2
		0 - 100	0-20

Table 3. Barthel Index, Activity, Scoring system at time of inclusion and today.

1.7 Diagnostic tests

In addition to the clinical neurological examination on admission, vital parameters as blood pressure, pulse and temperature are taken, neuroimaging by CT or MRI are done and supplementary tests including laboratory tests and electrocardiogram (ECG) are performed to assure the right diagnosis and to assess relevant comorbidity.

Laboratory tests on admission included in the time the study was performed complete blood count, electrolytes, renal and liver function tests, blood glucose, markers of cardiac ischemia and coagulation status including international normalized ratio (INR) in the patients using warfarin. An ECG is performed to assess the heart rhythm and to identify cardiac comorbidity and arrhythmias. Blood pressure is monitored and treated to ensure optimal cerebral perfusion, hyperthermia and infections are treated. Doppler ultrasonography is performed to evaluate precerebral vessel status.

1.7.1 Radiologic neuroimaging

Diagnostic neuroimaging has undoubtedly a key role in the diagnosis of acute stroke. Primarily it is important to exclude acute hemorrhage, as it is a contraindication to intravenous thrombolysis. Radiological imaging by CT or MRI is also able to detect very early ischemia, and to quantify and discriminate irreversibly infarcted core tissue from salvageable penumbra and demonstrate areas of hemorrhagic transformation. Furthermore, large vessel occlusions can be diagnosed, in order to select patients for endovascular treatment.

1.7.1.1 Computed tomography (CT)

CT is the most commonly used initial imaging of acute stroke worldwide; it is quickly and easily accessible within most hospitals and provides sufficient information about stroke type, localization of the stroke and also about contraindications to treatment as intravenous thrombolysis. The scans can be performed with iodinated contrast injected in a peripheral vessel, for perfusion (CTP) and angiographic (CTA) scans that provide information about brain perfusion, penumbral tissue and vessel status.

1.7.1.2 Magnetic resonance imaging (MRI)

MRI is increasingly used in the diagnosis and management of stroke as it has a high sensitivity and specificity to detect ischemic changes (48). Yet, despite of increasing accessibility in the larger hospitals it is still not broadly used due to lacking routines, economic reasons and contraindications. Often MRI investigations are perceived as more time consuming and thus an initial CT investigation is preferred. In minor hospitals accessibility of MRI is the main challenge. Multimodal imaging protocols including diffusion-weighted series, perfusion imaging (MRP), FLAIR (fluid-attenuated inversion recovery), mismatch calculations, T2* and intracranial angiography (MRA) results in accurate diagnostics for acute ischemic stroke patients.

1.7.2 Carotid ultrasound

Carotid Doppler ultrasound is used to image the main precerebral vessels (the internal carotid artery and the vertebral artery) and to identify any disturbance of flow, velocity or structural lesions indicating stenosis and occlusions. Atherosclerotic carotid artery disease is an important risk factor for ischemic stroke and the risk of clinical symptoms increases with the degree of stenosis (49). The sensitivity and specificity for identifying a 50% stenosis and a >70% stenosis are 90-98% and 88-94% respectively (50). The ultrasound procedure is less accurate than CTA and MRA but it is cheap, non-invasive and can be easily performed bedside.

Stenoses are being measured according to different criteria locally and globally, as there exist no common consensus. The most common criteria are the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria (51) and European Carotid Surgery Trial (ECST) criteria (52). In these trials the percentage of stenosis was calculated as a ratio of diameters measured from angiograms. The diameter of the residual lumen in the stenosis was compared with the diameter of the normal ICA lumen distal to the bulb in the NASCET method, as the ECST method compared it with an estimate of the diameter of the artery at the point of stenosis (Figure 1.). Both trials also showed the benefit of performing carotid endarterectomy in patients with significant ICA disease. The relationship between the ECST values and the NASCET values closely approximate: $ECST+\% = 0.6 \text{ NASCET } \% + 40 \%$ (53).

All ultrasound scanners use pulsed Doppler to measure the blood velocities measured as peak systolic velocity (PSV) and end-diastolic velocity (ESV). The PSV ratio has been widely used to assess the grade of stenosis. The ratio (PSVR) of peak systolic ICA velocity to peak systolic CCA velocity can be calculated. Peak systolic ICA to end-diastolic CCA ratio is called the St Mary's Ratio. If these measurements are in agreement, diagnostic confidence is gained (Table 4.) (54-57). All velocities should be measured at a Doppler angle of 45-60°.

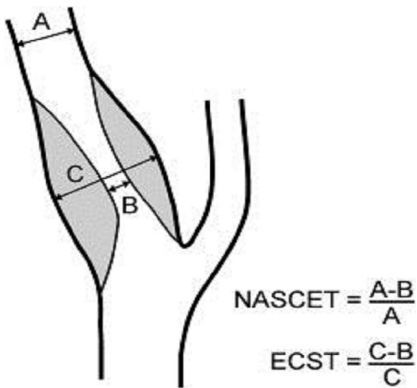


Figure 1. Diagram of ICA stenosis showing the NASCET and ECST methods of calculating percentage diameter stenosis (54).

NASCET Percentage stenosis	ECST Percentage stenosis	Internal carotid peak systolic velocity (cm/sec)	Peak systolic velocity ratio (PSVR) ICAPSV/CCAPSV	St Mary's Ratio ICAPSV/CCAEDV	Post stenotic PSV (cm/sec)
<50	<70	<125	<2	<8	
50-59	70	>125	2-4	8-10	
60-69	75			11-13	
70-79	80	>230	>4	14-21	>50
80-89	90			22-29	<50
>90 (but less than near occlusion)	95	>400	>5	>30	<30
Near occlusion		High, low – string flow	Variable	Variable	
Occlusion	Occlusion	No flow	Not applicable	Not applicable	

Table 4. Different Doppler grading systems for determining internal carotid stenosis (54-57).

1.8 Risk factors for stroke

1.8.1 Age

Age is the most important risk factor for stroke. The likelihood of having a stroke nearly doubles every 10 years after age 55. Although strokes are more common in the elderly, young people can suffer a stroke as well. In a review by Appelroos and colleagues with over 30 000 patients in 19 countries, the mean age at first stroke was 68.8 years for men (variations from 60.8 years in Ukraine to 75.3 years in Norway) and 72.9 years for women (65.3 in Malta to 80.4 in Sweden) (58). In Norway, the mean age at stroke in 2015 was 75 years (77.5 years for women and 71.9 years for men), and 90% of the stroke patients were >60 years old (18).

1.8.2 Sex

Women have a higher lifetime risk of stroke than men. In the Framingham Health Study (FHS), lifetime risk of stroke among those 55-75 years of age was 1 in 5 for women and 1 in 6 for men (24). This difference is explained by longer life expectancy for women. The age-specific incidence rates are substantially lower in women in the younger and middle-age groups. As most strokes occur in the higher age groups the longer life expectancy is leveling out this effect, leading to overall incidence rates in women that are approximately equal to or even higher than those in men (58-60). The stroke mortality for women in general is generally higher than for men. This is again caused by an age effect due to higher life expectancy in women. In the age group <85 years more men are dying of a stroke (26, 59).

Female-specific risk factors for stroke include: Pregnancy, history of preeclampsia/eclampsia or gestational diabetes (61), oral contraceptive use (especially when combined with smoking and migraine with aura) (62), post-menopausal hormone therapy (63) and oophorectomy (64). Preeclampsia is associated with increased stroke

risk and may be mediated by later risk of hypertension and diabetes mellitus (DM) (65), also genetic factors play a role (66).

1.8.3 Hypertension

Long term hypertension (defined as a systolic blood pressure ≥ 140 mmHg and/or a diastolic pressure ≥ 90 mmHg) is the leading cause of stroke and the most significant controllable risk factor for stroke (67-69). The pathogenesis of hypertension is conceived as multifactorial: genetic, environmental and behavioral factors are interplaying. Antihypertensive treatment is effective for all age groups and races and is decreasing stroke risk and the risk of other cardiovascular events. In a large meta-analysis by Law and colleagues a 41% (33% to 48%) risk reduction in stroke when reducing systolic blood pressure with 10 mm Hg systolic or diastolic blood pressure with 5 mm Hg was confirmed (70). This evidence is supported by other studies concluding that intensive blood pressure (BP) control (systolic blood pressure (SBP) < 120 mmHg) results in a significantly lower risk of stroke, less recurrent strokes and minor cardiovascular events in general (71-73). It is recommended that blood pressure should be lower than 130/80 mmHg, especially in people at high risk of stroke (74).

1.8.4 Smoking/Tobacco use

Cigarette smoking is a substantial risk factor for ischemic stroke and (75, 76), with a dose-response relationship between smoking and risk of stroke across age groups (77). The nicotine and carbon monoxide in cigarette smoke damage the cardiovascular system and increases the stroke risk equally for men and women (77). Cigarette smoking combined with use of oral contraceptives can greatly increase the risk of stroke (78), as also smoking combined with hypertension (79). Even passive smoking is proved to be a dose-responsive risk factor for stroke and thus all smoking stroke patients should be encouraged to quit smoking (80).

1.8.5 Diabetes mellitus

Diabetes mellitus (DM) is an independent risk factor for stroke. As many people with diabetes also have other risk factors as high blood pressure, high blood cholesterol or overweight, the cumulative risk factors elevate stroke risk even further. Diabetes mellitus increases ischemic stroke risk at all ages, but the risk is most prominent before 65 years (81). Diabetes mellitus more than doubles the risk for stroke, and it is estimated that almost 20% of patients with diabetes mellitus will die of a stroke. Several mechanisms are hypothesized, including direct neurotoxicity and systemic consequences (82, 83). The duration of diabetes mellitus is associated with the cumulative stroke risk and it is estimated that the stroke risk increases by 3% each year of diabetes duration (81). In case of prediabetes, fasting hyperglycemia is associated with stroke (84).

For patients with diabetes mellitus multifactorial treatment can decrease stroke risk significantly (85). In patients with DM type 2, there is no evidence that reduced glycaemia decreases the short-term risk of macrovascular events, including stroke (86). A glycated hemoglobin goal of <7.0% has been recommended by the American Diabetes Association to prevent long-term microangiopathic complications, but the impact on long-term risk of stroke is unclear. A meta-analysis by Zhang showed that intensive control of glucose compared with usual care had no effect on incident stroke but in a stratified analyses, a beneficial effect was seen in patients with diabetes mellitus and a body mass index (BMI) >30 kg/m² (87). Aggressive BP lowering in patients with diabetes mellitus and hypertension reduces stroke incidence in all age groups (88).

1.8.6 Atrial Fibrillation

Atrial fibrillation (AF), an arrhythmic heart rhythm characterized by rapid and irregular beating is associated with a 4- to 5-fold increased risk of ischemic stroke. The lack of organized atrial contraction can lead to stagnation of blood in the left

atrium or left atrial appendage (LAA). Through thrombus formation and thrombus mobilization these blood clots can be spilt away with the blood flow, causing emboli leading to TIA or stroke (89). It is assumed that AF is common and underestimated in patients with cryptogenic stroke (90), and screening for arrhythmias is therefore recommended in this patient group (91, 92).

1.8.7 Heredity/family history

A documented parental ischemic stroke is associated with a 3-fold increased stroke risk in offspring also after adjustment for other known stroke risk factors (93), and parental history of several other CVDs increase the risk for new CVDs (27, 94). The gene regions/genes found to be important, are involved in a variety of different functions related to atherosclerosis, coronary artery disease, atrial fibrillation, blood pressure, coagulation, carotid plaque formation and neuroinflammation i.a. (35). Certain stroke subtypes have higher estimated heritability to certain gene loci according to genome-wide association studies. For large-vessel disease robust association have been reported with gene loci HDAC9 and TSPAN2 (95-97), for cardioembolic stroke PTX2 and ZFHX3 (97, 98) and for small-vessel disease FOXF2 (99); Apoprotein E alleles are also clearly associated with ICH (100). A trend is emerging toward higher heritability in women and younger stroke patients (98, 101).

1.8.8 Hypercholesterolemia

Hypercholesterolemia, also called dyslipidemia, is the presence of high levels of cholesterol or blood lipids. Lipoproteins transports the cholesterol particles, and are classified by their density: very low density lipoprotein (VLDL), low density lipoprotein (LDL), intermediate density lipoprotein (IDL) and high density lipoprotein (HDL) (102). Elevated levels of the lipoproteins other than HDL (termed non-HDL cholesterol) and LDL in the blood may be a consequence of diet, obesity, inherited (genetic) diseases (such as LDL receptor mutations in familial

hypercholesterolemia), or the presence of other diseases such as diabetes or an underactive thyroid (103). Elevated levels of particularly LDL-cholesterol are associated with an increased risk of atherosclerosis, coronary heart disease (104) and stroke (105). In contrast, higher levels of HDL cholesterol are protective and elevated total cholesterol is inversely associated with hemorrhagic stroke (106). Statin therapy reducing LDL-cholesterol can safely reduce the 5-year incidence of major coronary events, coronary revascularization, and stroke by about one fifth per mmol/L reduction in LDL cholesterol (107). This effect is largely irrespective of the initial lipid profile or other presenting characteristics (108). However, the association of each subfraction has shown inconsistent results on ischemic and hemorrhagic stroke risk (105, 109-112) and several studies consider the fortunate effect of statins not being caused by its cholesterol lowering properties (113).

1.8.9 Carotid stenosis

The precerebral carotid vessels, most importantly the common carotid artery and internal carotid artery supply the brain with blood. These vessels and especially the carotid bifurcation are common sites for atherosclerosis due to increased turbulence and areas of lower shear force (114) which gives room for an inflammatory buildup of an atheromatous plaque that narrows the lumen and influences the blood flow. The plaque can be stable and asymptomatic or it can be a source of embolization. The correlation between severity of stenosis and ischemic events is not perfect, and molecular and cellular processes responsible for plaque composition might be more important for the risk of stroke. Thickening of the internal artery layer (the intima media) is the first sign of subclinical atherosclerosis, and the inflammatory process of atherosclerosis is shown to be most prominent at the early stages (115).

Calcification, incidence of lipid core and fibrous cap and intraplaque hemorrhage are characteristics that determine plaque stability (116, 117). Large resultant plaques extruding into the vessel lumen pose not only an impedance to flow but serve as a

nidus for thrombus formation. In addition, plaque instability and plaque rupture can propagate thromboembolic debris and lead to cerebrovascular events.

The Framingham Heart Study noted a prevalence of significant (>50%) carotid stenosis of 7% in woman and 9% in males ranging between 66–93 years (118). Atherosclerotic carotid artery disease is an important risk factor for ischemic stroke and the risk of clinical symptoms increases with the degree of narrowing (49), which can be measured by duplex ultrasound. The sensitivity and specificity for identifying a 50% stenosis and a >70% stenosis is high, 90-98% and 88-94% respectively (50). There exist various grading criteria; the most common used being the NASCET and ESCT (91, 91) criteria (1.7.2 Carotid ultrasound). In the Asymptomatic Carotid Stenosis Risk Stratification study (ACRSRS), the risk of stroke increased from 0.6% per year in patients with mild stenosis (50%–69%) to 1.9% per year in patients with severe stenosis ($\geq 90\%$) (119). An increase in the degree of stenosis by 2 or 3 categories (50%–69%; 70%–89%; 90%–99%; and 100%) over 1 year was related to an increase in the incidence of ipsilateral ischemic events by a factor of 4 or 7, respectively (120). Some plaque features as echolucency, intraplaque hemorrhage and a thin fibrous cap are associated with significantly higher stroke risk (121). The stroke risk of carotid stenosis is enhanced if other risk factors as hypertension, smoking or diabetes coexist (27). Carotid stenosis $\geq 25\%$ is also associated with a 2.2-fold increased risk of cerebral microbleeds (122). Roughly, carotid stenoses can be graded in mild (<50%), moderate (50 - 79 %), severe (80 – 99%) stenosis and subtotal/total occlusion (100%).

1.8.10 Hyperhomocysteinemia

A high level of the non-protein α -amino acid homocysteine in the blood ($\geq 15,0$ $\mu\text{mol/L}$) (hyperhomocysteinemia) makes the cells more prone to endothelial injury. This can lead to inflammation in the blood vessels, which in turn can lead to atherogenesis and can result in ischemic injury (123). Hyperhomocysteinemia is thereby a known risk factor for stroke (124), but its relevance is debated. Smaller

studies have shown that elevated homocysteine (HCY) promotes cerebral, arterial, and venous thrombosis and may predispose to premature atherosclerosis, craniocervical arterial dissection (125), increased oxidative stress (126) and can be assessed with long-term mortality (127). Even though hyperhomocysteinemia is generally acknowledged as a treatable risk factor for atherothrombotic diseases and stroke, the current guidelines (128) do not recommend routine screening.

1.8.11 Renal impairment

It is known that chronic kidney disease is a risk factor for stroke (129). A meta-analysis of >280 000 patients showed a 43% increased incident stroke risk among patients with a glomerular filtration ratio (GFR) <60 mL/min (130), which is confirmed in other studies (131). Although GFR is routinely measured in clinical practice, proteinuria and albuminuria are better predictors of stroke risk in patients with manifest kidney disease (132). As subtle renal impairment (high normal serum creatinine) is a marker of increased cerebrovascular disease risk (133) and is associated with other relevant prognostic risk factors (hypertension, age, diabetes, heart failure), leading to the claim that renal impairment should be included in cerebrovascular risk scores (134). Renal impairment before suffering a stroke is also associated with worse clinical outcome (135).

1.8.12 Inflammation

Proinflammatory conditions, including acute and chronic infections, have been associated with an increased stroke risk. The risk of stroke is increased both in the acute and in the chronic phase of a wide spectrum of inflammatory conditions, and it is suggested that the inflammatory response rather than the condition itself is responsible for the increased risk (136). Different inflammatory mechanisms are deemed to play a role in the different stroke subtypes. This hypothesis is based on the observation that high levels of various immune system markers and acute phase

reactants in otherwise healthy individuals have been associated with stroke subtypes. C-reactive protein, IL-6, and lipoprotein-associated phospholipase A2 are some of the inflammatory markers that have been linked to stroke risk and prognosis (136). Multiple epidemiological studies have demonstrated that these markers are associated with increased risk of stroke, but the value of these markers in a clinical setting has not yet been proven.

1.8.13 Anemia

Anemia, a decrease of red blood cells or hemoglobin in the blood seems to have a clear association with cerebrovascular events. On one hand there is a direct connection between blood supply and tissue oxygen delivery, on the other hand there seems to be a link between anemia and new onset atrial fibrillation (137). Yet, anemia independently increases the risk of thromboembolic events as it is considered a hyperkinetic state which disturbs endothelial adhesion molecules that may lead to thrombus formation. Furthermore, blood flow augmentation and turbulence may result in the migration of a thrombus thus facilitating artery-to-artery embolism (138). Anemia on admission increases mortality and decreases functional improvement through increase of complications impeding stroke rehabilitation (139, 140). Furthermore, reduced blood hemoglobin levels impair oxygen delivery to the brain and hinder neurological improvement. Reduced blood hemoglobin level is a predictor of short and long-term mortality after stroke (141). Anemia due to the genetic disorder sickle cell anemia is a risk factor for strokes, especially in children and young patients (142, 143).

1.8.14 Other risk factors

Other risk factors influencing stroke risk not discussed here are core health behavior as physical inactivity, nutrition and obesity. In addition, medical conditions as sleep apnea and metabolic syndrome, as well as different psychosocial factors are possible

risk factors, increasing stroke risk especially when combined with any other risk factors (27).

1.9 Stroke treatment

1.9.1 Acute stroke treatment

Today, acute treatment of ischemic stroke means earliest possible reperfusion of the occluded artery accompanied by general supportive care and treatment of acute complications.

In 1995 there was a paradigm shift when intravenous thrombolysis (IVT) with rt-PA was introduced and occlusions could be treated effectively (144). Prior to this, the treatment was mainly supportive. IVT is considered as safe and effective treatment when administered within 4.5 hours after symptom onset (145, 146). Endovascular treatment (EVT) with mechanical intra-arterial thrombectomy should be administered in case of large vessel occlusions (147, 148).

1.9.2 Supportive stroke treatment

General supportive care is provided for all stroke patients, independently of treatment with IVT or EVT (149). Generally, it is strongly recommended that all stroke patients are treated in specialized stroke centers (150) as this enhances functional outcome for all patients. According to current AHA guidelines (151) and national guidelines (152) the following factors are in focus:

Hypoxia: Treatment with supplementary oxygen is provided when the oxygen saturation is below 95% (153).

Circulation: The blood pressure (BP) is optimized to ensure adequate blood flow and oxygen deliverance to the brain (154), and is lowered when BP is $>220/120$ mmHg. In patients retrieving intravenous thrombolysis or endovascular treatment blood pressure below 185/110mmHg is recommended. In case of ICH, the current recommendations are that the systolic BP should be <180 mmHg (155), but intense treatment to secure systolic BT <140 mmHg seems to be safe (155). Hypovolemia and blood glucose are monitored and quickly corrected with intravenous fluids and insulin or glucose as needed (156). Both hypo- and hyperglycemia at acute stroke predict poor outcome (157, 158) and should be avoided.

Heart function: Electrocardiogram (ECG) is performed for detection of atrial fibrillation or other potentially serious cardiac arrhythmias that might need emergency therapy.

Hyperthermia: is associated with poor outcome (159) and body temperature should be lowered.

1.9.3 Secondary stroke prevention

Depending on the cause of the stroke, secondary prevention treatment with medication is recommended for most patients. Life-long antithrombotic medication and cholesterol lowering statins are recommended for most patients, in addition to antihypertensive and antidiabetic medication if needed. For patients with cardio-embolic strokes, anticoagulation therapy is indicated, and for ICH blood-thinning medication is contradicted in most cases (152, 160). Initiation or optimization of BP therapy is indicated in stroke patients where the BP is not falling spontaneously ≤ 140 mm Hg systolic or ≤ 90 mm Hg diastolic during the first days. Although these BP values are given as a reference the individual BP goals in each patient and the level of reduction from pretreatment baseline values remain uncertain and should be individualized (128). For all patients, general lifestyle advice and changes are recommended, i.e. smoking cessation, increasing daily physical activity, weight

reduction, healthy low-sodium diet and avoidance of excessive alcohol intake – all of which alone or combined reduce the risk for recurrent strokes or CVD (161-166).

1.9.3.1 Antithrombotic medication

In patients with a non-cardioembolic stroke or TIA antiplatelet drugs are recommended. There are three approved antithrombotic drugs in Norway: Aspirin, combination aspirin/dipyridamole and clopidogrel); on average, these agents reduce the relative risk (RR) of stroke, myocardial infarction (MI), or death by ~22% (128, 167). In patients with non-valvular atrial fibrillation whether paroxysmal or permanent, oral anticoagulants are the first choice, either VKA or direct oral anticoagulants (DOAC) as apixaban/dabigatran/rivaroxaban/edoxaban (128).

1.9.3.2 Statins

Blood cholesterol is effectively lowered by daily use of oral 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins). Statin therapy is recommended to reduce the risk of stroke and cardiovascular events among patients with ischemic stroke or TIA. The statin effect is assumed to be most notable in case of atherosclerotic disease with embolization from carotid or aortic vessels (107, 128). The Norwegian national guidelines recommend statin treatment if LDL cholesterol is $>2.0\text{mmol/l}$ (152). Stroke patients already using statins at admission have better outcome and lower mortality (168). As the SPARCL trial revealed, achieving a LDL cholesterol level of $<70\text{ mg/dL}$ (1.8mmol/l) by using statins was related to a 28% reduction in risk of stroke without a significant increase in the risk of hemorrhagic stroke. Additionally, stroke and TIA patients with $\geq 50\%$ reduction in LDL cholesterol had a 35% reduction in combined risk of nonfatal and fatal stroke (169).

1.10 Mortality

A decline in stroke mortality and morbidity over the past decades is seen in all age groups, for both sexes, and for all racial/ethnic groups. It mirrors the achievements in acute stroke therapy, diagnostics and rehabilitation. These achievements are of major importance for global health, and entail a huge economic potential. The decline in mortality results from reduced incidence of stroke and lower case-fatality rates combined. This happened concurrent with cardiovascular risk factor control interventions. Although it appears to be difficult to credit a specific risk factor control, efforts in hypertension control initiated in the 1970s appear to have had the most substantial influence on the accelerated decline in stroke mortality (29). Although implemented later, diabetes mellitus and dyslipidemia control in addition to smoking cessation programs, particularly in combination with treatment of hypertension, also appear to have contributed to the decline in stroke mortality.

The mortality after stroke increases generally with higher age and after recurrent strokes. Thus, the stroke mortality is in general higher for women due to older age at stroke (59). In the lower age group (<85 years) the mortality is higher for men (26). Hemorrhagic strokes are associated with higher mortality and morbidity as compared to ischemic strokes, although they are in total less common (6).

Data from the Atherosclerosis Risk in Communities (ARIC) study showed that the cumulative all-cause mortality rate after a stroke was 10.5% at 30 days, 21.2% at 1 year, 39.8% at 5 years, and 58.4% at the end of the 24 years of follow-up (112). Mortality rates were higher after an incident hemorrhagic stroke (67.9%) than after an ischemic stroke (57.4%). Age-adjusted mortality after an incident stroke decreased over time (absolute decrease of 8.1 deaths per 100 strokes after 10 years), which was mainly attributed to the decrease in mortality among those aged ≤ 65 years (absolute decrease of 14.2 deaths per 100 strokes after 10 years) (170, 171).

1.11 Nursing home placement after stroke

Stroke is the single most important factor for complex disability in adults (172) and therewith as well the main cause for nursing home placement (NHP) (172-174). In 2010, 39.4 million DALYs were lost because of ischemic stroke and 62.8 million because of hemorrhagic stroke (64% and 85%, respectively (175)). After a stroke, roughly two-thirds of the patients are consequently disabled in some way (176).

About half of the surviving stroke patients can be directly discharged from hospital to their homes; the other half has a remaining disability requiring special services or even institutionalized care (173, 177-179). Yet, reported institutionalization rates after stroke vary widely by population, setting, and duration of follow-up: 13 - 45% of stroke patients are institutionalized directly after hospitalization (177, 180, 181) and 10 - 83% within a period of 5 years (15, 23, 178, 182, 183). Age and initial stroke severity are the main predictors for NHP after stroke (180, 184-186), as well as age, cognitive and functional impairment that are the main predictors in the general population (187, 188).

2. Aims of the study

2.1 Paper I

Statin therapy has an established role in the treatment of atherosclerotic disease and in secondary stroke prevention, and is especially important in carotid stenosis. The aim was to analyse the effect of statin treatment on long-term survival, by analysing the long-term survival rates and the causes of deaths of patients with carotid artery stenosis on statin treatment compared to matched statin naïve patients.

2.2 Paper II

Stroke is one of the leading causes of mortality worldwide, and understanding the risk factors associated with long-term stroke mortality is important. The aims were to compare long-term mortality of patients with acute stroke compared to a geographically age- and sex-matched, stroke-free control. We aimed to identify possible risk factors for long-term mortality in the stroke patient group.

2.3 Paper III

Stroke is one of the leading causes for NHP, but the prognosis of NHP for the patients that can be discharged home after stroke is not known. The aims in study three were to analyse the proportion of stroke patients that could initially be discharged home, and to further analyse the need for NHP in this group compared to a matched stroke free control group. Additionally, we aimed to assess risk factors for permanent NHP.

3. Subjects and methods

3.1 Patients and follow up

The Stavanger University Hospital (SUS) serves the county of Rogaland with a population of approximately 330 000 inhabitants, distributed between 29 smaller municipalities at the time of inclusion. The municipality of Stavanger was the largest with approximately 130 000 inhabitants. All study participants in paper one were referred consecutively as outpatients to the cerebrovascular ultrasound laboratory between 1994 to 1996. The patients were followed until death or the end of the observational period on May 1st, 2011.

All patients consecutively admitted to the stroke unit at SUS between January 1, 1996 and March 31, 2004 were included in the study in paper two (n=1472). These patients were followed until death or until May 31, 2012. All patients belonging to the municipality of Stavanger from this cohort were studied further regarding NHP in paper three (n=452), and were followed until death or until May 31, 2012.

3.2 Controls

The control group in study two and three was obtained from the National Population Register of Statistics in Norway. Reference individuals were acquired arbitrarily from the general population but were individually matched 1:1 according to sex, age and local residency on the same year the patient was hospitalized for stroke. To have a stroke-free control group the hospital files for the control individuals were examined for stroke diagnoses. Individuals with a stroke or a transient ischemic attack (TIA) diagnosis (431, 434, 435 in ICD-8 and ICD-9, I61 and I63 with subclasses in ICD-10) were excluded from the control group along with their corresponding index patient. No clinical data was available for the control group.

3.3 Ethics

The studies were conducted in accordance with the Declaration of Helsinki. All studies were approved by the Regional Ethics Committee for Medical Research Ethics, University of Bergen.

3.4 Clinical evaluation

The patients in paper 1 were examined with an ultrasound procedure at their first visit. At this baseline examination demographic and clinical data from the participants were collected and a cholesterol measurement was done. The ultrasound procedure is described below.

For the patients in paper two and three, a neurologic examination including SSS (40) was performed at admission as well as diagnostic neuroimaging with a CT scan. Data on patient's functional status before and after the stroke (Barthel Index) were assembled by stroke nurses in collaboration with the patient and their families (47). Data regarding occupation, marital status and residency at the time of stroke were compiled. Pre-existing cardiovascular disease, hypertension, smoking, diabetes, heredity for cardiovascular disease and blood pressure on admission were also noted. The index stroke type was further classified into cerebral infarction, intracerebral hemorrhage or TIA.

3.5 Laboratory analyses

For study two and three routine hematological analyses were performed at admission including hemoglobin, leucocytes, creatinine, electrolytes, CRP and INR. The first day after admission, fasting glucose and cholesterol, HDL cholesterol, LDL

cholesterol, triglycerides, homocysteine and HbA1c were analyzed at the hospital's laboratories.

3.6 ECG

For study two and three an electrocardiogram was performed at admission in all patients to identify cardiac pathology or arrhythmias such as atrial fibrillation.

3.7 Ultrasound Doppler

All sonographic examinations were performed by the same, experienced neurologist using a EME/Nicolet 2000 TC 2020 Doppler device with a transducer with 2 and 4 MHz frequencies in pulsed and continuous wave Doppler modes for complete peripheral vascular applications. All velocities were measured at a Doppler angle of 45-60°. The degree of stenosis was calculated by the peak systolic velocity ratio (54, 189).

3.8 Nursing home placement

In the city of Stavanger which is the largest municipality in the region with about 130 000 inhabitants, a digital register ("CosDoc") exists, containing complete information regarding temporary and permanent nursing home placement (NHP). Reliable information about NHP was to a large part lacking in the other municipalities in the region, and thus we only included patients registered in the city of Stavanger at the time of their stroke along with their matched controls. As there existed several different types of rehabilitation settings and temporary nursing home placements, we have only recorded the dates for permanent nursing home placement.

3.9 Statistical analysis

The basic statistical analyses were performed in IBM SPSS 18.0 and 22.0 (SPSS Inc, Chicago, IL, USA) and in R. Chi-squared test was used for categorical variables and one-way analysis of variance (ANOVA) to compare means for continuous variables. For survival analysis Kaplan-Meier curves were calculated and logistic regression analysis was used to assess the impact of risk factors affecting time until NHP. Kaplan-Meier plots illustrate the observed survival in patients and controls.

In paper two, Chi-squared tests were used to compare the survivor fraction between both groups at different time points. A shared frailty model was fitted in R (package survival, function coxph for Cox regression) to compare overall mortality between the stroke patients and their matched controls. The analysis of risk factors for death among stroke survivors, was also performed using coxph. All continuous variables were standardized before the analysis, and covariates contributing little to the fit of the model were removed from the model. The effects of predictors with evident non-linear effects were modelled by multivariable fractional polynomials using the package mfp. The proportional hazards assumption was tested by examination of Schoenfeld residuals by function cox.zph. Models were compared by likelihood ratio tests. All excluded variables were reintroduced into the final model to check for confounding effects.

For all analyses, we considered a p-value <0.05 to be significant.

4. Results

4.1 Paper I

The study showed a markedly increased long-term survival among patients with carotid stenosis taking statins compared to statin-naïve patients, also after controlling for age and cholesterol-levels at baseline. The effect was long-lasting and had a persistent increase over time. The causes of deaths were nearly identical in both groups; thus we hypothesize that the increased survival is caused by more general statin effects than due to a reduction of vascular risk factors.

4.2 Paper II

In this study, we followed stroke patients surviving the first year after acute stroke for up to 16.4 years. We compared their mortality risk with a matched, stroke free control group. At the end of the study period, 51.7% of the patients and 32.7% of the stroke free control individuals had died (HR of 2.2 (CI 1.9 – 2.5) ($p < 0.001$)). The mortality risk stayed continually increased for at least 10 years. Regression analyses indicated that in addition to the known risk factors age, diabetes, and stroke severity also low cholesterol and hemoglobin as well as elevated creatinine and homocysteine at index stroke were associated with increased long-term mortality. These factors are modifiable and should possibly be followed more intensely after patient dismissal.

4.3 Paper III

In this study, we show that the majority of our stroke patients (88.7%) were able to live at home either directly after their stroke or after initial short-term rehabilitation.

Yet, stroke patients discharged to their homes needed NHP significantly more frequently and earlier than the stroke free, age and sex matched control population from the same geographical area (29.9% vs 18.5%). After initial hospital discharge, only age was a risk factor for NHP. The length of the stay in the nursing home facilities did not differ compared to non-stroke controls. Both groups stayed less than 1.8 years (1.6 vs 1.7 years, respectively) in the facilities until death.

5. Discussion

Stroke affects about 17 million people each year globally, a number projected to increase because of demographic changes and an aging population where the risk of stroke is greatest.

The Global Burden of Disease study has calculated that between 1990 and 2010 despite of falling age-standardized rates of incident stroke, the number of strokes occurring worldwide increased by 68% and the number of stroke survivors by 84% (31). This increase in stroke prevalence is caused by improvements in acute stroke care such as organized inpatient stroke unit-based care (29) and the implementation of IVT and EVT leading to a greater proportion of patients surviving the acute stroke episode (31). As treatment of stroke patients improves continuously, long term follow-up studies of stroke patients acknowledge the fact that treatment conditions have changed during the observational period. This is the case for the patients included in our studies as well.

In present not only more patients survive their strokes, but they survive with fewer handicaps, leading to improved survival and increased prevalence of stroke. As consequence of this increased survival stroke survivors and their families have to deal with the long-term consequences of stroke, including physical disability, cognitive impairment (190), fatigue, and psychological problems such as depression and anxiety. Stroke is shifting away from being a major killer to become a long-term (chronic) condition with multiple impacts for individuals, health systems and society (31, 191). Therefore, research regarding long-term consequences of stroke is of utmost interest. However, although data about long term follow up are emerging increasingly, most studies have a relatively short follow-up.

In the papers included in this thesis we have focused on long-term survival and risk factors that influence mortality over time in both stroke survivors and in patients with carotid stenosis. We have compared stroke patients to matched, stroke-free controls

from the general population. In the following chapters the papers are discussed one by one.

5.1 Paper I

5.1.1 Mortality

In the first paper, we analyzed whether statin use prolongs survival in patients with carotid stenosis. This is of special interest as statin use has shown to decrease stroke rates in patients with general atherosclerosis and especially patients with carotid stenosis (192-194). We could show that statin use in patients with carotid stenosis was, independently of preexistent cholesterol levels, associated with increased survival (88.3% of the patients that never used statin had died, compared to only 39.6% in the statin group, $p < 0.001$). The difference in mortality remained highly significant over time also after adjusting for age and current smoking. Yet, statin use did not influence the causes of death and did not reduce the proportion of vascular causes of death. This could indicate that the extended survival of statin users could be explained by other, more general effects of statins. These results are consistent with other studies (113). The statin effect on mortality in our study was long-lasting (> 10 years) and showed a persistent increase over time. This indicates possible benefits of statin treatment beyond today's knowledge and extended use for a wider patient group should be investigated. However, our results are limited by the fact that treatment stratification was not performed by random and confounding by indication cannot be excluded, although the study team did not influence the decision to start statin treatment during baseline examination or follow-up. Yet, this kind of study could not have been done today, because present guidelines strongly recommend statin use when atherosclerosis is documented or lipid measurements exceed certain values (128, 195), especially in patients with carotid stenosis (196). The guidelines were not as rigorous at the time of patient inclusion and the use of statins was not

mandatory. In earlier conducted studies in the same study population the use of statin medication (simvastatin) was shown to prevent progression of carotid artery stenosis, and maybe even reverse stenosis grade (197, 198). In other studies, in patients with moderate to severe carotid stenosis, optimal medical treatment including statin treatment failed to reverse stenosis grade and in some studies as well no effect on disease progression was seen (199, 200). Different effects of statin medication on carotid stenosis may be based on different pathophysiological processes ongoing in different stenosis grades, inflammatory ones being more pronounced in the early stages. Carotid stenosis leading to transient or permanent neurologic or retinal symptoms within the preceding 6 months are deemed symptomatic and require prompt noninvasive evaluation and treatment (195, 201). Landmark trials have proven carotid endarterectomy (CEA) superior to medical therapy for stroke prevention in symptomatic lesions. Carotid artery stenting (CAS) is found to be non-inferior to CEA, and the strength of the combined data has led to a class I recommendation for CEA or CAS in patients with high grade symptomatic carotid stenosis, provided the risk of perioperative events is acceptable (195, 202). In our study, the patients with ICA occlusion or symptomatic lesion were excluded.

Our results show that statin treatment in patients with carotid stenosis led to significantly increased survival, independently of their preexistent cholesterol levels. Surprisingly, we did not see a decline in cardiovascular related deaths which adds evidence to the present belief that rather “pleiotropic than cholesterol-lowering effects” are contributing. “Pleiotropic effects” discussed to contribute are effects on endothelial function, cell proliferation, inflammatory response, immunological reactions, platelet function, and lipid oxidation. These "pleiotropic actions" are independent of the cholesterol lowering ones, and appear to be neuroprotective (113, 203). Fitting to this concept statin use has shown to be beneficial as in sepsis (204), cerebral hemorrhages (205), carotid surgery (202) and possibly also as add-on treatment in depression as well (206).

5.2 Paper II

5.2.1 Long-term mortality

Most studies investigating long-term consequences of stroke include data from the first month after dismissal and thereby mix short-term and long-term consequences. To be able to analyze only the long-term mortality of initial stroke survivors we did not include patients dying within the first year after their stroke. Previous studies about long-term mortality in stroke patients are limited by the fact that they have a relatively short observational period. There are not many studies reporting 5-10 years outcome (15, 207, 208) and those few with more than 10 years of follow-up have only small numbers of included patients (209-211).

We followed stroke patients that survived the first year for up to 16.4 years, and compared them to an age- and sex matched stroke-free control group. The mean age at stroke was 66.8 years. At the end of the study, 51.7% of all patients had died compared to 32.7% of the stroke free controls (Risk Ratio (RR) 1.58 (CI 1.43 – 1.75, $p < 0.001$)). The follow up time of the included stroke patients differed substantially due to varying inclusion times and time points of deaths: After 5 years follow up 57.3% of the patients had died compared to 37.4% of the stroke free controls. After 12 years the corresponding numbers were 72.5% for stroke patients and 53% for controls. Thus, our mortality numbers are in line with earlier conducted studies where the cumulative case fatality was estimated around 40% to 60% 5 years (212-214) and >80% 14 years after acute stroke (215, 216).

5.2.2 Risk factors

The risk of death is greatest in the first few weeks after the stroke. The resulting brain injury and secondary complications, partly due to immobilization, are believed to be the main causes for the short-term mortality (217-219). Risk factors predicting long-

term mortality in stroke patients have been less understood (211, 220), but there is evidence that other factors are of importance in predicting long term mortality. The most important risk factor for mortality after stroke, early and late, is undoubtedly age (29). For early mortality (within the first year) the severity of the stroke and cardiovascular risk factors such as atrial fibrillation (217, 221) are prominent risk factors. For long-term mortality smoking, male gender and diabetes have been postulated as risk factors (159, 222, 223).

In our study age, diabetes and stroke severity predicts mortality in stroke survivors also in the long run. Yet, atrial fibrillation, previous stroke and hemorrhagic stroke were not significant. In our study, relatively few patients with atrial fibrillation and hemorrhagic stroke were included, thus the lack of statistical significance should not be overrated. Atrial fibrillation, often underdiagnosed and asymptomatic, is an independent risk factor and is thought to generate new strokes and thus increase the ischemic burden (224, 225). The same mechanism is discussed for patients with earlier strokes of other etiology and for the aging brain: Decreasing functional capacity of the brain and increasing burden of the disease lead to functional decline (226) and increase risk of mortality (227).

Diabetes is shown to be a predictor of increased mortality in stroke (228). The mechanism is thought to be microangiopathic, leading to small vessel disease. Diabetes is also associated with other relevant risk factors (hypertension, age, diabetes, heart failure), jointly increasing the risk for mortality. In patients with diabetes mellitus renal impairment is seen more frequently and we can show in our study that renal impairment is an independent risk factor for long-term mortality. Consequently, we propose that even slightly impaired creatinine found at index stroke should be followed more closely to avoid worsening of renal function. It has even been proposed that renal impairment should be included in cerebrovascular risk scores (134), but which level of impairment is discussed.

Hyperlipidemia is a well defined and modifiable risk factor for ischemic stroke (229) and treatment with statins is recommended. However, several studies in vitro (230,

231) and in patients report a beneficial role of hyperlipidemia through mechanisms of neuroprotection (232-234) leading to a less severe neurological deficit and a decreased mortality. Furthermore, naturally low cholesterol levels - not as a consequence of statin use – are associated with increased short-term mortality (235, 236). Following these observations it is considered that it is a statin effect and not the low cholesterol itself predicting a better outcome (237). At the time of inclusion in our study, statins were not routinely prescribed to stroke patients with low cholesterol values, and thus a confounding effect cannot be totally excluded.

Hyperhomocysteinemia is in some studies suggested to be a risk factor for stroke (238, 239), but the latest AHA-guidelines do not recommend routine screening (128). Metabolic vitamin B12-deficiency is common among elderly (239). However, there seems to be increasing evidence that treatment with folic acid and vitamin B12 (which is the treatment for hyperhomocysteinemia) reduces the risk for stroke (240-242). Yet, some studies fail to confirm a possible beneficial effect of homocysteine lowering vitamin B-complex therapy on cardiovascular outcome, including stroke (195, 243).

Anemia at the time of stroke worsens outcome and increases mortality (141). Reduced levels of blood hemoglobin are hypothesized to impair oxygen delivery to the brain and hinder neurological improvement and repair mechanisms during and after a stroke (139). We can confirm these findings in our study and advocate that even low-grade anemia should be followed up in stroke patients.

5.2.3 Strengths and limitations

The included patient cohort is representative for stroke patients in Norway, but it is not an epidemiological cohort study. The prospective patient inclusion, the long observational period, the large number of included patients, the strength of the statistical model and the control group with stroke free, sex and geographically matched control persons strengthens the validity of the results. However, the lack of

medical data in the control group and missing follow-up investigations are limiting the results. Additionally, some variables for the risk factors analyses were not available retrospectively and therefore some patients had to be excluded from these analyses.

5.3 Paper III

5.3.1 Nursing home placement

Permanent institutionalization after stroke is related to the presence of hemiplegia (244) especially if it occurs in addition to functional and cognitive impairment, which are the strongest predictors of NH admission in general. A functional dependency in 3 or more ADL areas is associated with higher odds for NHP (245). In our material, 10.6% of the stroke patients were directly admitted to permanent NH, and 88.7% could be discharged to their homes either directly (44.7%) or after temporary rehabilitation (44.0%). These numbers are somewhat lower than those in other reports (181, 185), yet institutionalization rates vary widely due to geographical and socioeconomic factors, family prepositions, access to further rehabilitation as well as distribution of health insurances. The intensity of rehabilitation is also known to influence necessity of ensuing NHP. Early supported discharge (ESD) increases chances that stroke patients can live at home after the initial stay on the stroke ward(246). As we do not have information about the intensity of rehabilitation that was performed we weren't able to make according correlations.

The stroke patients initially discharged home stayed at an increased risk for permanent NHP compared to the age- and sex matched stroke free controls (37.2% versus 19.9%). They were also admitted to NH earlier than their controls, and they died earlier confirming that a stroke is a major risk factor for death.

The different stroke types in this study were not associated with increased risk for NHP, but in general it is assumed that hemorrhagic strokes and ischemic strokes caused by atrial fibrillation are associated with bad outcome (247, 248).

In all patient groups in this study, the length of the stay in NH was equal and in general quite short: only 1.6 years (SD 1.9) until death (or study end) for all patients and 1.5 years for the stroke-free controls. This might be caused by the similarity of the overall criteria for NHP for all types of patients in the Norwegian Health Care system, based on an individual assessment of the combination of cognitive and functional impairment accompanied by lack of support and assistance in daily living.

The age at NHP for all stroke patients was equal, 81 years for the patients directly admitted after their stroke and 82.2 years for the patients primarily dismissed home, while stroke-free controls were admitted first at higher age (85.5 years). The interplay of stroke-related disability and age seems to be the most plausible explanation for this age difference.

5.3.2 Risk factors

Most studies describe NHP only as a discharge destination and the final length of the placement is not known. We show here that the length of NHP did not differ between the stroke patients and the stroke free controls, indicating that incurring costs for NHP for each individual may not differ significantly. However, as significantly more stroke patients are admitted to nursing home there is no doubt that the economic burden is relevant for society. Identifying risk factors for NHP is important to reduce this burden by aiming to prolong the time staying at home for each patient.

In this study only the patients' first stroke was considered and cognitive assessment was not registered. Several studies affirm that recurrent strokes, cognitive deficits, depression and low physical activity level prior to stroke are risk factors linked to NHP after stroke (178). Health insurance status is an issue in some countries (185), providing unequal possibilities for rehabilitation and care but is not an issue in

Norway where all inhabitants have the same rights through the Norwegian Health Care system.

Patients that could be discharged home were not surprisingly younger, they cohabited more often and their functional status before the stroke was better. Their strokes were less severe, and they suffered less atrial fibrillation and cardiovascular comorbidity. But they smoked more. Smoking is negatively associated with direct NHP or NHP at a later time point. This tobacco paradox is found as well in patients with acute coronary syndrome (249) and inconsistently found in earlier studies, most probably explained by residual confounding.

However, regression analyses showed that only age ($p<0.001$) and severity of the stroke ($p=0.014$) were significant predictors for NHP when all risk factors were included. For the patients initially discharged to their homes only age was a factor influencing NHP (OR 1.053-1.125, $p<0.001$).

5.3.3 Strengths and limitations

The long observational period, the prospective patient inclusion, the stroke free, age- and sex matched control group and the complete nursing home registry in our community strengthen the results. Significant advances have been made over the last decades in terms of treatment protocols and secondary prevention changing the prospects of disability and mortality and this must be considered. The lack of follow-up investigations and medical data of the control group are clear limitations of the study. In addition, the health care systems policy for care of the elderly with impairments has changed over the study period.

6. General conclusions

Paper I: We have followed long-term mortality in patients with carotid stenosis, comparing patients on statin treatment with statin-naïve patients. Statin treatment was associated with markedly increased long-term survival. This effect was long-lasting and with a persistent increase over time and may be caused by a more general statin effect.

Paper II: We analyzed the long-term survival in stroke survivors and compared it to sex- and age matched, stroke free controls from the same geographical area. Stroke patients had a significantly increased mortality. The mortality risk stayed continually increased for at least 10 years. Beside of the known risk factors age, diabetes, and stroke severity also low cholesterol and hemoglobin as well as elevated creatinine and homocysteine at index stroke were risk factors for mortality.

Paper III: We analyzed the proportion of stroke survivors needing permanent NHP as compared to stroke-free matched controls. Almost 90% of the stroke patients could be dismissed home after their stroke. Stroke patients initially discharged home were admitted to a nursing home significantly more often and earlier than their controls – but only age was a risk factor for NHP. The stroke patients did not stay longer than other patients in the nursing homes, which is in accordance with the health care systems general policy that the total situation with general functional and cognitive impairment is the most important cause for NHP.

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8. Original publications

Treatment with statins improves long-term survival in individuals with carotid artery stenosis

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Statin therapy has an established role in the treatment of arterio-sclerotic disease and in secondary stroke prevention. Up to 20% of relative risk reduction in major vascular events per 1 mmol/L decrease in LDL cholesterol is reported [1]. Atherosclerotic carotid stenosis is an important risk factor for stroke and the inflammatory process of arteriosclerosis is shown to be most pronounced in the early stages. We have earlier shown that statin treatment may prevent and even reverse the progression of stenosis in the internal carotid artery (ICA) over time [2,3]. We have now 10 years later investigated survival and causes of death during the long-term follow-up of the same patients with and without statin treatment.

From August 1st 1994 until December 31st 1997 all outpatients referred consecutively to the cerebrovascular ultrasound laboratory of the Stavanger University Hospital were evaluated for study participation and were included independently of the reason for admission. Inclusion criteria are described in detail previously (2). All included patients ($n=291$) had a stenosis $\geq 40\%$ in one or both ICA as determined with ultrasound examinations. Patients with endarterectomy of the stenosis ($n=32$) or occlusion of the carotid artery ($n=20$) were excluded from the study, as were the 9 patients where the collected data were considered not reliable. 230 patients were included in this study, informed consent given at first examination. The use of statins was at this time not established as mandatory in patients with atherosclerotic disease, and the decision to start with statin therapy was at the discretion of their general practitioner and not influenced by the study team before baseline examination and during follow-up. The study patients were followed until death or to the end of the observation period on May 1st, 2011. During this period information on statin treatment was collected through the hospital files and information from the patients' general practitioner. Information on date and cause of death as the primary outcome variable in this study was obtained as ICD-10 classification codes from the Norwegian Cause of Death Registry. The study was conducted in accordance with the Declaration of Helsinki; the protocol was approved by the Ethics committee of the University of Bergen. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

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Based on the collected information on statin use, the 230 patients were categorized into three groups: 1. Never used statins, 2. Statin treatment, and 3. Part time statin treatment. Patients in the first group, Never used statins ($n=60$) had not been treated with a lipid lowering drug during the study period. Patients, who were classified as on Statin treatment ($n=111$), were already on statin treatment at baseline and stayed on statin therapy throughout the study period. Patients classified as Part time statin treatment ($n=59$) were on statin therapy for a shorter or longer time period but not the whole study period. Of these 59 patients 54 (91.5%) started after baseline while 5 patients were on the drug at baseline and stopped treatment with statins later on.

Baseline characteristics and causes of death were examined using one-way analysis of variance (ANOVA) and chi-squared test as appropriate. We used Cox proportional hazards models to elaborate associations with mortality. In all Cox models, patients were followed from baseline to death, or to May 1st 2011, for those still alive. Age at baseline and sex were entered as covariates. In order to strictly exclude an age effect on mortality we additionally age-matched patients on statin therapy with patients never on such therapy individually and repeated the Cox hazard models. This procedure yields equal group distributions regarding age. Statistical analyses were performed using the statistical software SPSS 18.02. *p*-Values less than 0.05 were considered statistically significant.

Of the 230 patients included at baseline, 125 (54.3%) had died at the end of the study period. The mean time from study inclusion to death was 12.8 years (range 1.5–16.8). Demographic and clinical variables at baseline are given in Table 1. There were no significant differences in gender, smoking habits, history of cardiovascular events, prevalence of diabetes or hypertension, or the degree of ICA stenosis. Patients on statin treatment were younger (67 years (SD 8.2) vs. 69.4 years (SD 7.7) in the Part time statin treatment group and 74.4 years (SD 8) in Never used statins group ($p<0.001$)), and had lower cholesterol levels at study start. As age at baseline was substantially different between the groups, a secondary analysis of individually matched persons from the groups Never used statins and Statin treatment was done. These two groups ($n=46$) were matched individually according to age at baseline (mean age 72.3 years (SD 7.9)). In these matched cohorts patients not using statins were more likely to smoke (45% vs. 19.5%, $p=0.004$) and had significantly higher cholesterol levels at baseline (6.23 vs. 4.99, $p<0.001$) (Table 2). Mortality rates differed markedly between patients on statin treatment and patients without statin treatment: In the patient group Never used statins 53 patients (88.3%) had died, while 44 patients (39.6%) in Statin treatment group and 28 patients (47.4%) in the Part time statin treatment group had died. The difference stayed highly significant after adjustment for age and cholesterol levels (Fig. 1). The Cox-regression showed that statin treatment was a significant predictor for lower mortality, with a hazard ratio (HR) of 0.27 (CI 0.16–0.44, $p<0.001$) for the Part time treatment group and a HR of 0.311 (CI 0.19–0.5, $p<0.001$) for the Statin treatment group. The difference in mortality between the two age-matched groups remained highly significant in this analysis after adjusting for age and current smoking (Fig. 2). Statin treatment was associated with a significant lower HR of mortality, HR=0.344 (CI 0.19–0.61, $p<0.001$). There were no significant differences in the causes of death in the different patient groups (Table 3).

Table 1
Demographic and clinical variables of the patient groups at baseline according to treatment with statins.

	All patients n = 230	Statin treatment n = 111	Part time treatment n = 59	Never used statins n = 60	p-Value
Mean age, years (SD)	69.5 (8.5)	67 (8.2)	69.4 (7.7)	74.4 (8)	<0.001
% females	53.5	57.7	49.2	50	0.46
% ever smoked	64.2	65.7	63.2	62	0.89
% current smoking	27.8	21.9	29.8	38	0.1
% hypertension	55.2	58.6	54.2	50	0.55
% diabetes mellitus	12.6	11.7	11.9	15	0.81
Mean total cholesterol mmol/l, baseline (SD)	5.57 (1.28)	4.9 (0.9)	6.3 (1.4)	6.3 (1.1)	<0.001
Mean degree carotid stenosis % (SD)	59.8 (12.3)	60.6 (14.2)	55.6 (11.6)	62.5 (15.6)	0.097
Previous cardiovascular event %	44.3	45.0	35.6	51.7	0.21

Statistical analysis: One way analysis of variance (ANOVA) and chi-squared test as appropriate.

In this study treatment with statins seems to markedly increase long-term survival in individuals with moderate to severe stenosis of the ICA but not due to a relative reduction in vascular causes of death. The Asymptomatic Carotid Artery Progression Study trial statins appeared to reduce the risk of mortality after 3 years of follow-up [4]. Subsequent studies confirm longer survival in patients on statin treatment [5–7] and in the large Heart Protection Study (HPS) a 14% proportional reduction in mortality among statin users was found [8]. The recent follow-up study with a secondary open study phase had a total mean observation time of 11.0 years [9] and the superior survival among the statin users in the blinded first study period was preserved but did not increase during the extended follow-up. Decreased mortality was caused by a reduction in vascular related causes of death, while non-vascular causes were only mildly reduced.

In the current study we have followed the patients for a mean of 12.8 years, and we found a markedly increased calculated survival among individuals taking statins during this long follow-up time when controlling for age and baseline cholesterol levels. In addition, as age is the most important predictor for death, the second analysis where patients with and without statins were matched individually for age confirmed the results and showed a marked favorable long-term survival in those using statins. The results from our study further strengthen the suggested reduced mortality by using statins and also show that the positive effect is not only long-lasting but also has a persistent increase in effect over time.

In our study the causes of death were nearly identical in both the treated and non-treated patient groups. The fact that there did not seem to be a selectively reduced mortality due to vascular causes, may indicate that the improved survival related to the use of statins could be caused by decreased mortality also from the other causes of death. Thus

the extended survival in patients on statin medication must be explained by other, more general effects of statins [10,11].

Current treatment guidelines emphasize the indication for statins in patients with high cholesterol levels and in patients with cardiovascular risk factors. Yet, the rather remarkable effects observed in the current study may indicate that a wider patient group could benefit from statin treatment. This probability could be examined in randomized controlled studies with elderly individuals that do not fulfill established criteria for treatment with statins.

The presented study has several limitations: Treatment stratification was not performed at random and confounding by indication cannot be excluded. Compliance is not measured and cholesterol levels during follow-up are missing.

In conclusion, we show a rather marked longer survival in patients with moderate to severe carotid stenosis being on statin medication as compared to patients not taking statins. It seems that a more general effect or maybe interplay of several additive beneficial effects of statins is causing the prolonged survival. These effects could potentially also be relevant in the general population with important consequences for health and survival.

Table 2
Age matched patient groups: Demographic and clinical variables at baseline according to treatment with statins.

	All patients n = 92	Statin treatment n = 46	Never used statins n = 46	p-Value
Mean age, years (SD)	72.3 (7.7)	72.3 (7.9)	72.3 (7.9)	0.98
% females	54.3	56.5	52.2	0.68
% ever smoked	57.1	52.3	62.5	0.34
% current smoking	29.8	15.9	45	0.004
% hypertension	53.3	63	43.5	0.06
% diabetes mellitus	17.4	17.4	17.4	1
Mean total cholesterol mmol/l (SD)	5.5 (1.07)	5.0 (0.8)	6.2 (1)	<0.001
Mean degree carotid stenosis % (SD)	62.8 (14.6)	62.7 (13.6)	62.8 (15.6)	0.67
Previous cardiovascular event %	47.8	47.8	47.8	1

Statistical analysis: One way analysis of variance (ANOVA) and chi-squared test as appropriate.

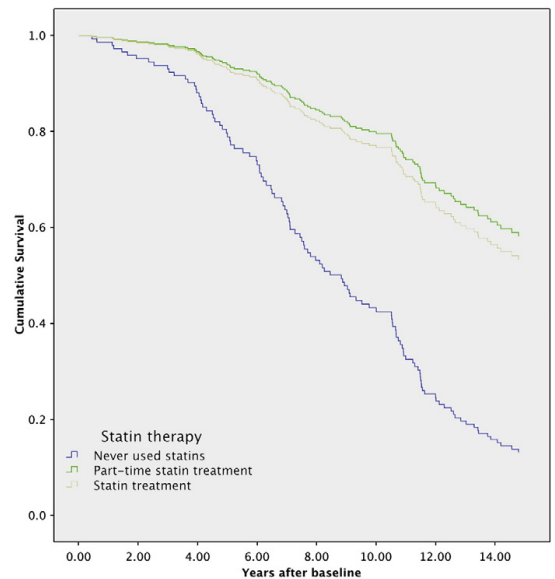


Fig. 1. Survival curves of the patient groups according to treatment with statins. The curves are adjusted for age and cholesterol levels.

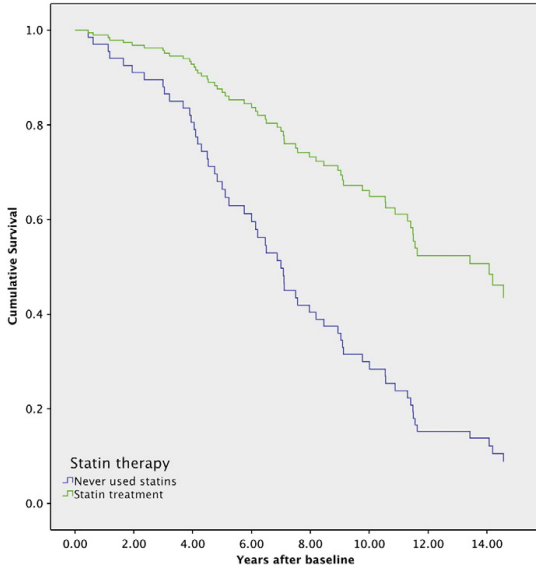


Fig. 2. Survival curves of the individually age-matched patient groups according to treatment with statins. The curves are adjusted for cholesterol levels and current smoking.

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None of the authors report any potential conflicts of interest, including related consultancies, shareholdings and funding grants.

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Table 3

Cause of death among all deceased patients according to treatment with statins or not.

	Statin treatment	Never used statins	p-Value
	n = 170, 72 deceased	n = 60, 53 deceased	
Cerebrovascular	9 (13%)	7 (13%)	0.56
Cardiovascular	30 (42%)	18 (34%)	0.38
Pulmonary related	7 (10%)	5 (9%)	0.96
Cancer related	17 (24%)	10 (19%)	0.53
Other	9 (13%)	13 (25%)	0.08

Statistical analysis: One way analysis of variance (ANOVA) and chi-squared test as appropriate.

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Long-Term Mortality and Its Risk Factors in Stroke Survivors

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and Martin Kurz, MD, PhD*†

Background: Stroke is one of the leading causes of mortality worldwide. Understanding the risk factors associated with stroke mortality is important to improve patient management. Few studies have examined long-term mortality and its associated predictive risk factors. *Methods:* We examined long-term mortality in 1137 patients with acute stroke and compared it to a geographically age- and sex-matched, stroke-free control group. We followed the stroke patients for as long as 16.4 years. In 1018 of these patients we assessed the effect of demographic, clinical, and hematological factors on mortality. *Results:* At the end of the study period, 51.7% of the patients and 32.7% of the stroke-free control individuals had died (hazard ratio 2.2, confidence interval 1.9-2.5, $P < .001$). A total of 72.5% of the patients and 53% of the controls with 12 years' follow-up ($n = 570$) had died ($P < .001$). Regression analyses indicate that, in addition to known risk factors such as age, diabetes, and stroke severity, both low cholesterol ($P < .001$) and hemoglobin ($P < .002$), hyperhomocysteinemia ($P = .005$), and elevated serum creatinine ($P < .001$) at index stroke are associated with increased long-term mortality. *Conclusions:* Stroke patients surviving the first year after stroke have a markedly increased mortality rate as seen in long-term follow-up. Furthermore, the results from this study indicate that changes in creatinine, homocysteine, and hemoglobin should be followed more carefully as standard practice after acute stroke. **Key Words:** Stroke—long-term—mortality—risk factors—homocysteine—creatinine.

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Introduction

Stroke is one of the leading causes of mortality worldwide with about 6 million people dying annually.¹ The risk of death from stroke is greatest in the first few weeks after the stroke. The resulting brain injury and secondary complications, due in part to immobilization,²⁻⁵ are the main causes for this short-term mortality.

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The risk factors for long-term mortality after stroke are less investigated,^{6,7} but existing evidence suggests that they differ in part from the short-term risk factors. Stroke severity, age, and cardiovascular risk factors^{2,4,7-9} are prominent predictors for mortality within the first year after stroke, whereas age, male gender, smoking, and diabetes are predictors for long-term mortality.¹⁰⁻¹² Few studies^{6,7} have investigated long-term mortality and compared the mortality rates of stroke patients with a stroke-free, age- and sex-matched control group from the general population living in the same geographical area. In young stroke survivors (18-50 years), the cumulative 20-year mortality compared to the general population exceeded expected mortality for decades after the initial stroke.¹³ Awareness of long-term mortality and its clinical predictors offers the opportunity to better regulate these risk factors in poststroke follow-up.

In the present study, we analyzed the long-term mortality rates in 1137 stroke patients hospitalized for stroke in the county of Rogaland, Norway, from 1996 to 2004. The patients were followed up for up to 16.4 years and

the mortality rates were compared to a stroke-free, age- and sex-matched group from the general population derived from the same geographical area. The risk factors predicting mortality were identified in the stroke patient group.

Materials and Method

Patients and Controls

All patients admitted to the stroke unit at Stavanger University Hospital between January 1, 1996, and March 31, 2004, were included in the study ($n = 1472$). At this time, the stroke unit was composed of 6 acute stroke beds that were continuously occupied by consecutive patients. If there was no capacity for new patients at the stroke unit, these patients were admitted to a general medical ward, but due to a lack of structured follow-up, these patients were not included in the study.

Demographic variables, medical history, and results of the radiological, laboratory, and clinical investigations were recorded on study inclusion (baseline) (Table 1). Neurological deficit was assessed clinically using the Scandinavian Stroke Scale (SSS).¹⁴

Information on death was collected through linkage to the National Population Register of Statistics (Statistics Norway) and the National Registry of Death, Norway, until May 31, 2012.

The control group was obtained from the National Population Register of Statistics. Reference individuals were acquired arbitrarily from the general population but were individually matched 1:1 according to sex, age (born on the same year as the index patient), and residency on the same year the patient was hospitalized for stroke.

Initially, 1472 acute stroke admissions were recorded. In case of repeated admissions during the study period, only the index stroke was taken into account. Thus, 82 multiple registrations were removed. Thirteen patients of foreign nationality were excluded as they were not registered in the National Population Register of Statistics. Furthermore, we excluded the patients who died within the first year of the stroke ($n = 72$) and their matched control persons as we aimed to assess long-term mortality (Fig 1).

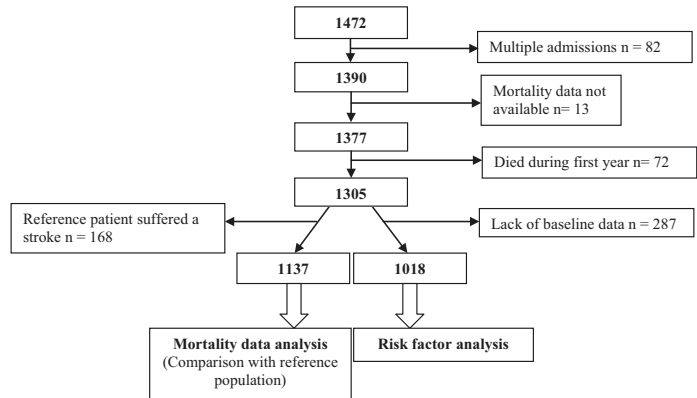
To have a stroke-free control group for the mortality analysis, we examined the hospital files of the control

Table 1. Demographic and clinical variables at baseline according to analysis

Variables	Factors	Mortality analysis	Missing	Risk factor analysis	Missing
		n = 1137	n	n = 1018	n
All patients	Mean age at inclusion (years)	66.8 (SD 14.3)	0	67.6 (SD 14.4)	0
	Dead at study end (%)	51.7	0	50.6	0
	Male (%)	54.6	0	54.1	0
	SSS score at admission (mean)	46.3 (SD 13.8)	409	46.0 (SD 14)	154
	SSS score at discharge (mean)	50.4 (SD 11.8)	424	50.2 (SD 12)	215
Cerebrovascular subtype	Infarct (%)	73.5	0	73.2	0
	Hemorrhage (%)	10.7	0	10.7	0
	TIA (%)	15.8	0	16.1	0
Risk factors	Previous cardiovascular event (%)	40.8	0	44.1	0
	Cardiovascular heredity (%)	18.3	245	18.4	7
	Hypercholesterolemia (%)	27.8	0	27.0	0
	Diabetes (%)	12.3	0	10.4	0
	Hypertension (%)	51.8	0	50.3	0
	Smoking (current or previous) (%)	39.8	47	41.2	47
	Atrial fibrillation (%)	9.3	238	10.9	140
	Carotid stenosis (%)	24.6	9	27.2	8
	Hyperhomocysteinemia (%)	22.0	239	23.5	1
	Mean values (SD)	Cholesterol value (mmol/L)	5.5 (1.2)	247	5.5 (1.2)
HDL cholesterol (mmol/L)		1.3 (.4)	282	1.3 (.4)	51
Triglyceride value (mmol/L)		1.4 (.7)	259	1.4 (.7)	25
Creatinine value (μ mol/L)		86.9 (25)	239	87.2 (25)	1
CRP at admission (mg/L)		16.3 (26)	238	16.7 (29)	0
Glucose value (mmol/L)		5.9 (1.5)	288	5.9 (1.5)	24
Cobalamine value (pmol/L)		328 (219)	371	330 (223)	154
Homocysteine value (μ mol/L)		13.6 (8)	400	13.9 (9.1)	183
Hemoglobine value (g/dL)		13.9 (1.5)	240	13.9 (1.5)	2

Abbreviations: CRP, C-reactive protein; HDL, high-density lipoprotein; SSS, Scandinavian Stroke Scale; TIA, transient ischemic attack; SD, standard deviation.

Figure 1. Flowchart explaining patient selection and study design.



group for stroke diagnoses. Individuals with a stroke or a transient ischemic attack (TIA) diagnosis (431, 434, 435 in the International Classification of Diseases [ICD]-8 and ICD-9, I61 and I63 with subclasses in ICD-10) ($n = 168$) were excluded from the control group along with their corresponding index patient for the mortality analysis. In the control group, no clinical data were available at baseline or during follow-up; thus, the analysis of long-term mortality was performed in 1137 patients and in an equal number of reference individuals (Fig 1).

The risk factor analyses were performed in 1018 stroke patients; 287 patients were excluded due to missing relevant data (Fig 1).

Clinical and Demographic Variables at Baseline

Data for age, gender, occupation, marital status, and residency at the time of stroke were compiled. Pre-existing cardiovascular disease, hypertension, smoking, diabetes, heredity for cardiovascular disease, presence of carotid artery stenosis measured by ultrasound,¹⁵ stroke severity (SSS), electrocardiogram findings, and blood pressure on admission were also noted. In addition blood levels of hemoglobin, cholesterol, triglycerides, high-density lipoprotein cholesterol, homocysteine (Hcy), creatinine, C-reactive protein, glucose, and HbA1c were recorded on admission. The index stroke type was further classified into cerebral infarction, intracerebral hemorrhage, or TIA.

Statistics

The basic statistical analyses were performed in IBM SPSS version 22 (IBM Corp., Armonk, NY, USA). A Kaplan–Meier plot illustrates the observed survival in patients and their matched controls. Chi-squared tests were used to compare the survivor fraction between both groups at different time points. A shared frailty model was fitted in R (R Core Team, Vienna, Austria) (package survival, function `coxph` for Cox regression) to compare overall mortality between the stroke patients and their matched

controls. The analysis of risk factors for death among stroke survivors was also performed using `coxph`. The risk factors considered are listed in Table 1. All continuous variables were standardized before the analysis, and covariates contributing little to the fit of the model were removed from the model. The effects of predictors with evident nonlinear effects were modeled by multivariable fractional polynomials using the package `mfp`. The proportional hazards assumption was tested by examination of Schoenfeld residuals by function `cox.zph`. Models were compared by likelihood ratio tests. All excluded variables were reintroduced into the final model to check for confounding effects. The predictive ability of the final model was estimated by Harrell's concordance/C-index, using the function `validate` in the `rms` package, with $B = 150$ bootstrap samples. For all analyses, we considered a P value less than .05 to be significant.

Ethics

The study was approved by the Regional Ethics Committee for Medical Research Ethics, University of Bergen. The authors have no disclosures.

Results

A total of 1137 patients were included in the mortality analysis and 1018 patients in the risk factor analysis. The demographic and clinical variables of the patients with acute stroke included in the different analyses are shown in Table 1. There were no statistically significant differences between the baseline data of the patient groups included in the analyses.

Mortality Analysis

Table 1 presents the characteristics of the 1137 patients included in the mortality analysis. The mean age at stroke was 66.8 years. Among the patients, 73.5% had an ischemic stroke, 10.7% had an intracerebral hemor-

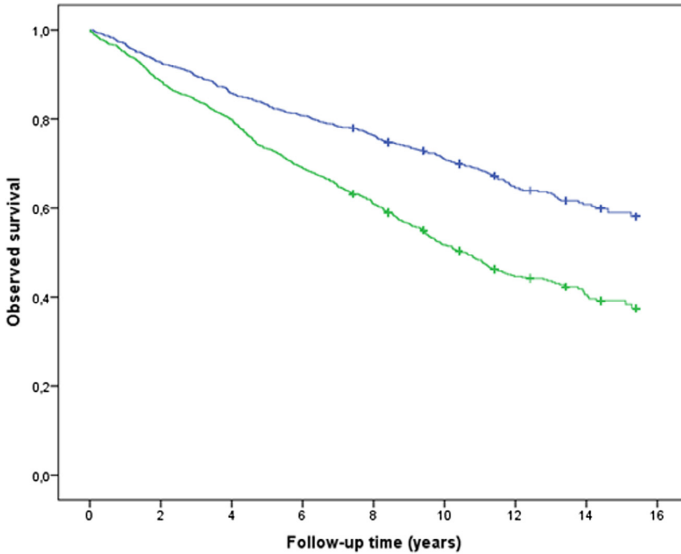


Figure 2. Kaplan–Meier curve illustrating survival for the stroke patients (green line) versus the stroke-free controls (blue line). (Color version of figure is available online.)

rhage, and 15.8% of the patients were diagnosed with a TIA. A total of 51.8% of the patients had hypertension, 12.3% diabetes, and 9.3% atrial fibrillation.

Among the stroke patients, 51.7% had died at the end of the study period, as compared to 32.7% of the controls (risk ratio [RR] = 1.58, 95% confidence interval [CI] 1.43–1.75, $P < .001$). The mortality rate for stroke patients compared to the controls was 2-fold higher (hazard ratio 2.2, CI 1.9–2.5) and stayed continuously elevated during the study period (Fig 2). Not all patients had an equal follow-up time due to different years of inclusion and varying times of death: 26.7% ($n = 303$) had died after 5 years as compared to 16.8% ($n = 191$) of the controls ($P < .001$); after 10 years of follow-up, the respective percentages of deaths were 57.3% ($n = 526$) and 37.4% ($n = 316$, $P < .001$), and after 12 years 72.5% ($n = 570$) and 53% ($n = 355$, $P < .001$).

Risk Factor Analysis

Table 1 shows the demographic and clinical data at the time of stroke including mean age at stroke (67.6 years), gender (54.1% male), and stroke type. At the end of the study, 50.6% of the stroke patients had died. Of all the variables recorded and included in the analysis, seven were significantly associated with death among stroke patients over time. As expected, age ($P < .001$), stroke severity (low SSS score) ($P < .001$), and diabetes ($P = .004$) were risk factors for mortality after stroke. The analyses also showed that hyperhomocysteinemia ($P = .005$), lower hemoglobin values ($P = .002$), elevated creatinine ($P < .001$),

Table 2. Factors associated with death among stroke patients surviving their first year

Variable	HR (95% CI)	P
Age	2.16 (1.9–2.4)	<.001
Cholesterol	.84 (.8–.9)	<.001
Creatinine	1.35 (1.1–1.6)	<.001
Hemoglobin*	1.04* (1.0–1.1)	.002
Diabetes	1.51 (1.1–2.0)	.004
Homocysteine	1.37 (1.1–1.7)	.005
SSS score 40–49	1.46 (1.1–1.9)	.003
SSS score 20–39	1.55 (1.2–2.0)	.001
SSS score 0–19	2.20 (1.6–3.1)	<.001

Abbreviations: CI, confidence interval; HR, hazard ratio; SSS, Scandinavian Stroke Scale.

Risk factors associated with increased mortality (HR) during long-term follow-up among stroke patients surviving the first year after stroke.

*Hemoglobin is transformed by $1/\sqrt{\cdot}$; that is, a lower hemoglobin level increases HR.

and hypocholesterolemia ($P < .001$) (Table 2) were risk factors associated with increased mortality over time. The impact of the risk factors stayed unchanged during the observational period.

Discussion

In the present study, we followed stroke patients surviving the first year after acute stroke and compared the mortality risk with a stroke-free control group for up to 16.4 years. At the end of the study period, 51.7% of the

patients and 32.7% of the stroke-free control individuals had died (hazard ratio 2.2, CI 1.9-2.5, $P < .001$). Regression analyses indicate that, in addition to known risk factors such as age, diabetes, and stroke severity, low cholesterol, hemoglobin, and elevated levels of creatinine and Hcy at index stroke were associated with increased long-term mortality. The mortality risk stayed consistently increased for at least 10 years.

Short-term mortality in stroke patients is intensively studied and is at its highest during the first 30 days.¹⁶ Patients surviving the first year also have a higher mortality risk than the general population, but few studies have long-term follow-up information. In the studies conducted, 12-year mortality rates vary from 15.7%¹⁷ in younger patients to as high as 86.5%¹⁸ in older patients. In younger patients, it is shown that the increased mortality rates continue across decades, implying that the underlying (vascular) disease process continues to elevate the risk for vascular disease throughout their lives.¹³ In our patients, 51.7% had died at the end of the study, but in the patients with a complete 12-year follow-up, 72.5% had died as compared to only 53% of the controls. Kaplan-Meier curves showed that the mortality was persistently increased during the entire study period.

The risk factor analysis confirmed that age, diabetes, and stroke severity are risk factors for increased mortality in stroke patients. Long-term mortality was also associated with elevated values of creatinine and Hcy as well as low cholesterol and hemoglobin levels at the time of the acute stroke. Ischemic heart disease, atrial fibrillation, hemorrhagic stroke, and previous stroke are suggested to be significant predictors for long-term mortality,⁷ but these were not found to be significant in our study.

Subtle renal impairment (high normal serum creatinine) is a marker of increased cerebrovascular disease risk¹⁹ and is associated with other relevant prognostic risk factors (hypertension, age, diabetes, heart failure), leading to the claim that renal impairment should be included in cerebrovascular risk scores.²⁰ This was supported by our data showing that even slightly elevated creatinine levels predict increased mortality over time.

Hyperhomocysteinemia is a known risk factor for stroke,²¹ but its relevance is debated. Smaller studies have shown that elevated Hcy promotes cerebral, arterial, and venous thrombosis, and may predispose to premature atherosclerosis, craniocervical arterial dissection,²² and increased oxidative stress²³ and can be assessed with long-term mortality.²⁴ Even though hyperhomocysteinemia is generally acknowledged as a treatable risk factor for atherothrombotic diseases and stroke, the latest guidelines from the American Heart Association²⁵ do not recommend routine screening. Our data suggest that hyperhomocysteinemia might be a risk factor for increased long-term mortality in acute stroke patients and we recommend further studies.

Hyperlipidemia is a well-defined and modifiable risk factor for ischemic stroke,²⁶ and the use of statins has been thought to contribute to a decline in stroke mortality.²⁷ Surprisingly, several studies also report a beneficial role of hyperlipidemia through mechanisms of neuroprotection^{28,29} leading to a less severe neurological deficit and thus a decreased mortality. However, low cholesterol levels without use of statins are associated with increased short-term mortality^{30,31}; therefore, it is only cholesterol reduction due to statin use that predicts a better functional outcome.^{28,32} Our findings suggest a possible negative association between hypercholesterolemia and mortality. At the time of inclusion in the present study, statins were not routinely prescribed to patients with low cholesterol at the time of stroke, which may have contributed to these results. Further trials are needed to assess the impact of dyslipidemia treatment on stroke incidence, outcomes, and mortality.

Diabetes is an established risk factor for stroke. Compared to nondiabetic patients, diabetic patients also have an increased risk of new vascular events and death after stroke.³³⁻³⁵ Literature suggests that hyperglycemia³⁶⁻³⁹ is a predictive factor for increased stroke mortality. Several mechanisms are hypothesized, including direct neurotoxicity and systemic consequences.^{40,41} Our results support that diabetes is a risk factor for long-term mortality after stroke.

Anemia appears to have a significant effect on the functional improvement and outcomes of ischemic stroke patients, as it may increase the rate of complications and decrease the efficacy of stroke rehabilitation.^{42,43} Reduced blood hemoglobin levels may impair oxygen delivery to the brain and hinder neurological improvement. A reduced blood hemoglobin level is seen as a predictor of short- and long-term mortality after stroke,^{44,45} in congruence with our findings.

This study has several limitations. Although the included patient cohort is representative of stroke patients in Norway, the study is not an epidemiological cohort study. Many advances have been made in terms of prevention and mortality of stroke since we began our study. Additionally, some variables for the risk factor analyses were not available retrospectively, and therefore some patients had to be excluded from these analyses. Furthermore, we lack medical data of the control group and follow-up investigations.

The prospective patient inclusion, the long observational period, the large number of included patients, the strength of the statistical model, and the control group with stroke-free, gender, and geographically matched control persons strengthen the validity of our results.

In conclusion, we have shown that stroke survivors after the first year after acute stroke have a persistently and nearly 2-fold increased risk of death during long-term follow-up. Several of the risk factors associated with long-term mortality can be modified. These factors, including

creatinine, hemoglobin, and Hcy, should possibly be followed up more intensely after patient discharge. We therefore recommend further studies in independent patient cohorts.

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III

The prognosis of stroke survivors primarily discharged to their homes

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Objectives: Stroke is one of the leading causes for nursing home placement (NHP). We have studied the prognosis and risk factors regarding NHP for stroke patients initially discharged to their homes.

Materials and methods: All stroke patients in the municipality of Stavanger, Norway, between January 1, 1996, and March 31, 2004, were included and followed until death or May 31, 2012. Time intervals for NHP and death were compared to an age- and sex-matched, stroke-free control cohort. Logistic regression analysis was used to assess risk factors for NHP.

Results: A total of 452 patients were included. A total of 48 patients (10.6%) were directly placed in a nursing home, while 401 patients (88.7%) were discharged to their homes; 180 patients (44.7%) directly and 221 patients (55.3%) after temporary rehabilitation. Of the patients discharged to their homes, 29.7% needed NHP at a later time point as compared to 19.9% of the controls ($P < .001$). Logistic regression analysis showed that only age ($P < .001$) was a risk factor for NHP. Stroke patients discharged home and stroke patients admitted directly to nursing home were significantly younger at time of NHP; stroke patients discharged home died significantly earlier than the controls.

Conclusions: Almost 90% of the stroke patients could be discharged to their homes, but they needed more often NHP in the long run than the stroke-free controls. Stroke patients discharged to their homes were younger at the time of NHP and death indicating that the stroke deficit may contribute to increased morbidity and mortality in this patient group.

KEYWORDS

discharge destination, nursing home, prognosis, stroke, stroke survivor

1 | INTRODUCTION

Stroke is one of the leading causes of mortality and morbidity. Worldwide, about six million people are dying annually,¹ and stroke is one of the leading causes for disability and institutionalization.² The prevalence of stroke is expected to increase significantly in the years ahead as the population above 65 years increases.³ In Norway, 15 000 people suffer a stroke annually and 55 000 Norwegians have had one or more strokes.⁴ Two-thirds are consequently disabled,⁵ and stroke is

conceived to be one of the main causes for disability and nursing home placement (NHP).

About half of the surviving stroke patients can be directly discharged from hospital to their homes; the other half has a remaining disability requiring special services or even institutionalized care at some point.^{2,6-9} Yet, reported institutionalization rates after stroke vary widely by population, setting, and duration of follow-up: 13-45% of stroke patients are institutionalized directly after hospitalization^{7,10,11} and 19-83% within a period of 5 years.^{8,12-14} Age and initial

stroke severity are the main predictors for NHP after stroke,^{10,15-17} as well as cognitive and functional impairment that are the main predictors in the general population.¹⁸

As stroke treatment is getting better more patients survive their stroke and live longer.^{19,20} Not much is known about the stroke patients initially discharged to their homes and if their prognosis regarding mortality and institutionalization differ compared to matched, stroke-free individuals. We have therefore examined the long-term need for institutionalization of stroke patients initially discharged to their homes. We have further elaborated the risk factors for NHP. The time intervals between hospital discharge, NHP, and death were calculated, and the proportions and time periods between NHP and death were compared.

2 | MATERIAL AND METHODS

2.1 | Patients and controls

All patients admitted to the stroke unit at Stavanger University Hospital between January 1, 1996, and March 31, 2004, were included in the study (n=1472). At this time, the stroke unit was comprised of six acute stroke beds that were continuously occupied by consecutive patients. If there was no capacity for new patients at the stroke unit, the patients were admitted to a general medical ward, and due to a lack of structured follow-up, these patients were not included in the study. All data were collected prospectively by stroke physicians and stroke nurses for internal quality assurance. Analyses for the current study were performed retrospectively. In the city of Stavanger which is the largest municipality in the region with about 130 000 inhabitants, a digital register ("CosDoc") contains complete information regarding temporary and permanent NHP. Reliable information about NHP was to a large part lacking in the other municipalities in the region, and thus, we only included patients registered in the city of Stavanger at the time of their stroke (n=563). The follow-up ended at May 31, 2012.

The control group was obtained from the National Population Register of Statistics (Statistics Norway). Reference individuals were acquired arbitrarily from the general population but individually matched 1:1 according to sex, age (born the same year as the index patient), and residency; the same year the patient was hospitalized for stroke. In the control group, no clinical data were available at baseline or during follow-up.

Information on death was collected through linkage to the National Population Register of Statistics (Statistics Norway) and the National Registry of Death, Norway, until May 31, 2012.

Patients discharged from the stroke unit without the diagnosis of stroke, intracerebral hemorrhage, or transient ischemic attack (TIA) (431, 434, 435 in ICD-8 and ICD-9, and I61 and I63 with subclasses in ICD-10) were excluded along with their matched controls (n=22). In case of repeated admissions during the study period, only the index stroke was taken into account, excluding 31 observations.

In order to have a stroke-free control group, we examined the hospital files of the control group for stroke diagnoses. Individuals with

a stroke or a TIA diagnosis (431, 434, 435 in ICD-8 and ICD-9, and I61 and I63 with subclasses in ICD-10) were excluded along with their corresponding index patient (n=58, 11.4%) leaving 452 patients and controls for analysis. Further, the patients were divided into stroke patients initially discharged to their homes (directly or after temporary rehabilitation) (n=401) and patients who were directly and permanently admitted to a nursing home (n=48).

2.2 | Clinical and demographic variables at baseline

Results of the radiological, laboratory, and clinical investigations were recorded on study inclusion (baseline) (Table 1). Data for age, gender, and cohabitation status were collected; data on functional status before stroke were assembled by stroke nurses in cooperation with the patient, the families, and caregivers to correctly estimate the patient's functional status (Barthel Index²¹). Preexisting cardiovascular disease, hypertension, diabetes, smoking, heredity for cardiovascular disease, presence of carotid artery stenosis measured by ultrasound, stroke severity (Scandinavian Stroke Scale²²), ECG findings, and blood pressure on admission were noted. In addition, blood levels of hemoglobin, cholesterol, triglycerides, HDL cholesterol, homocysteine, creatinine, CRP, glucose, and HbA1c were recorded on admission. The index stroke type was classified into cerebral infarction, intracerebral hemorrhage (ICH), or TIA.

2.3 | Statistics

The statistical analyses were performed in IBM SPSS 22.0 (SPSS Inc, Chicago, IL, USA). Chi-squared test was used for categorical variables and one-way ANOVA to compare means for continuous variables. For survival analysis, Kaplan-Meier curves were calculated and logistic regression analysis was used to assess the impact of risk factors affecting NHP. The significance level was set to .05.

2.4 | Ethics

The study was approved by the Regional Ethics Committee for Medical Research Ethics, University of Bergen.

3 | RESULTS

We included 452 acute stroke patients in the analyses. The mean follow-up time after the acute stroke was 7.5 years (range 0-15.4). Mean age at stroke was 69 years (range 24.6-96.1). A total of 202 patients (44.7%) were discharged directly from the stroke unit to their homes and 199 (44.0%) after temporary rehabilitation in different rehabilitation units or other wards. Three patients (0.7%) died in the stroke unit, and 48 patients (10.6%) were directly and permanently discharged to a nursing home. Baseline data of the patients including risk factors on admission and stroke subtypes are shown in Table 1.

In univariate analysis, the patients initially discharged to their homes had more often TIA (16.5% vs 2.1%, $P<.001$), less often ICH

TABLE 1 Demographic data at baseline for all patients, the patients that were discharged directly to a nursing home (NH) and for the patients that were discharged home either directly or after rehabilitation

	All patients n=452	Patients directly admitted to NH (n=48)	Patients discharged home (n=401)	P-value
	Missing	Missing	Missing	
Gender n (% male)	235 (52)	22 (45.8)	211 (52.6)	.37
Mean age in years at stroke (range)	69.4 (24.6-96)	80.8 (8.6)	67.6 (13.5)	<.001
Cohabitation status (not alone) n (%)	264 (58.4)	16 (33.3)	246 (61.8)	.006
Stroke subtype				
Ischemic stroke n (%)	331 (73.2)	33 (68.8)	296 (73.8)	<.001
ICH n (%)	54 (11.9)	14 (29.2)	39 (9.7)	<.001
TIA n (%)	67 (14.8)	1 (2.1)	66 (16.5)	<.001
Hypertension n (%)	254 (56.2)	29 (60.4)	223 (55.6)	.53
Diabetes mellitus n (%)	58 (12.8)	10 (20.8)	47 (11.7)	.07
Smoking (current/previous) n (%)	173 (38.3)	6 (12.5)	167 (41.6)	<.001
Previous cardiovascular disease n (%)	154 (34.1)	21 (43.8)	133 (33.2)	.043
Previous stroke/TIA/ICH n (%)	83 (18.4)	7 (14.6)	76 (19)	.83
Carotid stenosis >60% n (%)	96 (21.2)	10 (20.8)	86 (21.4)	.13
Atrial Fibrillation n (%)	33 (7.3)	102	7 (14.6)	.003
Stroke severity by SSS mean (SD)	45.05 (13.6)	12	47 (12.2)	.008
Barthel index before stroke mean (SD)	91.2 (22.1)	75	92.6 (19.4)	<.001

TABLE 2 Demographic data at baseline for the 401 patients that were discharged home divided into the patients that needed nursing home (NH) later on and those who did not

	Patients discharged home, later to NH (n=120)	Missing	Patients not admitted to NH (n= 281)	Missing	P-value
Gender n (% male)	54 (45)	0	157 (55.9)	0	.04
Mean age in years at stroke (SD)	76.4 (8.3)	0	64.5 (13.4)	0	<.001
Cohabitation status (living alone) n (%)	57 (48.3)	2	86 (31.7)	10	<.001
Stroke subtype - Ischemic stroke n (%)	92 (76.7)	0	204 (72.6)	0	.36
ICH n (%)	13 (10.8)	0	26 (9.3)	0	.35
TIA n (%)	15 (12.5)	0	51 (18.1)	0	.24
Hypertension n (%)	78 (65)	0	145 (51.6)	0	.01
Diabetes mellitus n (%)	16 (13.3)	0	31 (11)	0	.51
Smoking (current/previous) n (%)	36 (32.1)	8	131 (50.8)	23	.001
Previous cardiovascular disease n (%)	44 (46.3)	25	89 (35.3)	29	.06
Previous stroke/TIA/ICH n (%)	28 (29.5)	0	48 (19)	1	.1
Carotid stenosis >60% n (%)	33 (28)	2	53 (18.9)	1	.07
Atrial Fibrillation n (%)	12 (13.3)	30	14 (6.3)	57	.06
Stroke severity by SSS mean (SD)	46.1 (10.7)	2	47.4 (12.8)	7	.33
Barthel index before stroke mean (SD)	88.4 (22)	16	94.4 (18)	39	.008

(9.7% vs 29.2% $P<.001$), less severe strokes (SSS 47 vs 29.2, $P=.008$), and they were younger (67.6 vs 80.8 years, $P<.001$) than the patients that were admitted directly to nursing homes. The patients initially discharged home also cohabited more (61.8% vs 33.3%, $P=.006$), had less previous cardiovascular disease (33.2% vs 43.8%, $P=.04$), and less atrial fibrillation (6.5% vs 14.6%, $P=.003$). Additionally, they had a better functional level before the stroke (Barthel index 92.6 vs 78.3, $P=.008$), yet they smoked more (41.6% vs 12.5%, $P<.001$).

Of the 401 stroke patients discharged to their homes 120 (29.9%) needed NHP during follow-up, compared to 74 persons (18.5%) in the stroke-free control group ($n=401$, $P<.001$).

Table 2 shows that for the patients initially discharged to their homes, age at stroke (76.4 vs 64.5 years, $P<.001$), female gender (45% male vs 56%, $P=.04$), cohabitation status (48.3% vs 31.7% living alone, $P<.001$), hypertension (65% vs 51.6%, $P=.01$), and functional level (Barthel Index 88.4 vs 94.4, $P=.002$) were associated with NHP at a later time point. Smoking was negatively associated with NHP (32.1% vs 50.8%, $P=.001$).

At the end of the study, a total of 168 stroke patients (37.2%) and 90 stroke-free controls (19.9%) had been permanently placed in a nursing home ($P<.001$). Fifty-four percent of the stroke patients ($n=244$) and 33.8% of the control individuals ($n=153$) had died at study end ($P<.001$). However, the same proportions of stroke patients and stroke-free controls placed in a nursing home had died (89.2% vs 86.7%, respectively, $P=.39$).

The mean time from stroke to NHP was 4.2 years and from stroke to death 5.0 years (Table 3). The stroke patients were younger than the stroke-free controls at the time of NHP, independently whether they were initially discharged to their homes or directly admitted to a nursing home (81 and 82.2 vs 85.5 years, $P=.004$) (Figure 1). The stroke patients were also significantly younger at death (80.6 vs 83.9 years,

respectively, $P=.001$). There was no difference in time from NHP to death when comparing stroke patients initially discharged to their homes and matched controls (1.7 vs 1.3 years, respectively, $P=.145$) (Table 3).

Regression analyses showed that only age ($P<.001$) and severity of the stroke ($P=.014$) were significant predictors for NHP when all factors were included. For the patients initially discharged to their homes, only age was a factor influencing NHP (OR 1.09, 95% C.I. for OR 1.053-1.125, $P<.001$).

Demographic data at baseline for all patients, the patients that were discharged directly to a nursing home (NH) and for the patients that were discharged home either directly or after rehabilitation.

Demographic data at baseline for the 401 patients that were discharged home divided into the patients that needed nursing home (NH) later on and those who did not.

Kaplan-Meier curves describing age at nursing home admission for the patients admitted directly after the stroke, the patients that were discharged home but needed nursing home later and the stroke-free controls.

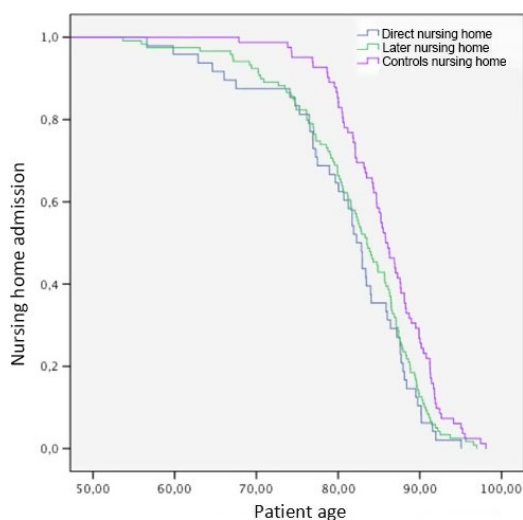
Time periods (years) from stroke to nursing home placement (NHP) and to death for the patient groups as described in Table 1, as well as the univariate analyses between the patient group discharged to their homes and their matched controls.

4 | DISCUSSION

In this study, we show that the majority of our stroke patients (88.7%) were able to live at home either directly after their stroke or after temporary rehabilitation. Yet, stroke patients discharged to their homes needed NHP significantly more frequently and earlier than the

TABLE 3 Time periods (years) from stroke to nursing home placement (NHP) and to death for the patient groups as described in Table 1, as well as the univariate analyses between the patient group discharged to their homes and their matched controls

	All patients n=452	Patients discharged directly to NH n=48	Patients discharged home n=401	Controls n=401	P-value
Dead at study end % (n)	54 (244)	97.9 (47)	48.1 (193)	31.4 (126)	<.001
Nursing Home Placement (NHP) % (n)	37.2 (168)	100 (48)	29.9 (120)	18.5 (74)	<.001
Mean age at NHP in years (SD)	81.8 (8.2)	81 (8.6)	82.2 (8.1)	85.5 (6.1)	.004
Mean age at death in years (SD)	80.6 (10.2)	83.3 (7.6) 47	80 (10.6) 193	83.9 (8.9)	.001
Mean time from stroke to NHP in years (SD) n	4.2 (3.6) 168	0.2 (0.3) 48	5.8 (3.1) 119		
Mean time from stroke to death in years (SD) n	5.0 (3.6) 244	2.3 (2.3) 47	5.7 (3.5) 153		
Mean time from NHP to death in years (SD) n	1.6 (1.9) 148	2.1 (2.3) 47	1.3 (1.7) 101	1.7 (2.1) 62	.15

**FIGURE 1** Kaplan-meier curves describing age at nursing home admission for the patients admitted directly after the stroke, the patients that were discharged home but needed nursing home later and the stroke-free controls

stroke-free, age- and sex-matched control population from the same geographical area (29.9% vs 18.5%).

In a recent study by Nguyen et al.,¹⁶ 78.2% of acute stroke patients were discharged to their homes and 21.8% placed in nursing homes. Internationally, institutionalization rates vary between 13% and 45% directly after hospitalization,^{10,11,16,23} and in our study, 10.6% were admitted directly to a nursing home after treatment for acute stroke. Variations in NHP are due to geographical and socioeconomic factors, family prepositions, access to further rehabilitation, and health insurances.^{16,24-26} Further, age and stroke severity are well-known

risk factors for institutionalization after stroke,^{10,17} and our findings are consistent for all stroke patients in this study. However, only age remained a significant risk factor for NHP in the patients that initially could be discharged home. It is known that rehabilitation organized as ESD (early supported discharge) increases the possibility for living at home,²⁷ but as we do not have detailed information about the level of rehabilitation in our patients, we have thus not included such an analysis in the current study.

Other factors known to be linked to NHP after stroke are cohabitation status, health insurance status, dysphagia, recurrent stroke, intracerebral bleedings, cognitive deficits, depression, and low physical activity level prior to stroke.^{8,10,12,22,24-26} In our study, only the patients' first stroke was taken into account and cognitive assessment was not registered. In univariate analysis, the patients that could be discharged home were younger, had less atrial fibrillation, and cardiovascular comorbidity, were not living alone but they smoked more. The strokes were less severe or TIAs, and the preexisting functional status was better. Atrial fibrillation is known to be a main reason for severe strokes that lead to worse outcome.²⁸

In patients initially discharged home, hypertension was predicting NHP in univariate analysis while atrial fibrillation was no longer significant. As we do not have follow-up investigations of the patients, these associations should be interpreted carefully. Yet future studies should prospectively follow patients and include regular medical investigations.

Smoking was negatively associated with NHP both in patients directly admitted to a nursing home or in patients placed in a nursing home at a later time point. This tobacco paradox is found as well in patients with acute coronary syndrome²⁹ and inconsistently found in earlier studies, most probably explained by residual confounding. Yet, it is shown that smokers do respond better to fibrinolytic therapy due to increased levels of circulating fibrinogen and tissue factor.³⁰

In both patient groups, stroke patients directly admitted to a nursing home and those initially discharged to their homes, the age at NHP

was similar (81 vs 82.2 years, respectively) while stroke-free controls were admitted significantly later to nursing home facilities (85.5 years) (Figure 1). Interplay of stroke-related disability and age seems to be the most plausible explanation for this age difference.

Although stroke patients in our study were placed more frequently and significantly earlier in a nursing home facility, the length of the stay in the facilities did not differ compared to non-stroke controls. Both groups stayed less than 1.8 years (1.6 vs 1.7 years, respectively) in the facilities until death. This may be explained by the similarity of the overall criteria for NHP for all types of patients in the Norwegian Health Care system, based on cognitive and/or functional impairment accompanied by lack of support and assistance in daily living.¹⁸ Especially, the first factors seem often to be exaggerated by a stroke.³¹

We have previously shown that stroke patients in general have an increased mortality.³² In the current study, we found that although far more patients directly placed in a nursing home had died, the age at death is significantly lower for the patients initially discharged to their home. As stroke patients discharged to their homes on average were 12.4 years younger at the time of their stroke, the stroke-related disability may lead to an earlier death as well in these patients, shortening time from stroke to death in general.

Most studies describe NHP only as a discharge destination, and the final length of the placement is not known. In our study, the length of NHP did not differ between stroke patients and stroke-free controls pointing to that incurring costs for NHP for each individual may not differ significantly. However as significantly more stroke patients are admitted to nursing home, there is no doubt that the economic burden is relevant for society. In order to reduce this burden and in order to prolong the time staying at home for each patient, it is important to identify risk factors for NHP.

The lack of follow-up investigation and the lack of medical data of the control group are limitations of this study as well as the lack of information regarding different levels of rehabilitation (especially ESD). Another limitation to consider is the significant advances that have been made over time in terms of treatment protocols and secondary prevention. In addition, the healthcare system's policy for care of the elderly with impairments has changed over the study period. Yet, the long observational period, the prospective patient inclusion, the stroke-free, age- and sex-matched control group, and the complete nursing home registry in our community strengthen the results from this study.

In conclusion, we have shown here that the majority of stroke survivors are able to be discharged to their homes, but they are still in need of earlier and more frequent NHP during follow-up than an age- and sex-matched, stroke-free control group. After initial hospital discharge, only age is found to be a risk factor for NHP. Length of NHP is equal in stroke and stroke-free individuals. In general, stroke survivors are at increased risk for death, also patients primarily discharged to their homes.

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CONFLICT OF INTEREST

None.

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