Clinical recurrent events after incident stroke or transient ischemic attack

Andrej Netland Khanevski

Thesis for the degree of Philosophiae Doctor (PhD)
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NORSTROKE
Bergen Stroke Research Group

Contents

Abbreviations

AF Atrial fibrillation

CCS Causative Classification System

CE Cardioembolism

CI Confidence interval

CISS Chinese Ischemic Stroke Subclassification

CNS Central nervous system

CT Computed tomography

DVT deep vein thrombosis

DWI Diffusion-weighted imaging

ECG Electrocardiography

GI Gastrointestinal

HR Hazard ratio

LAA Large artery atherosclerosis

ICAD Intracranial atherosclerotic disease

ICD-10 International Classification of Diseases, Tenth Revision

ICH Intracerebral hemorrhage

MRI Magnetic resonance imaging

mRS Modified Rankin scale

NIHSS National Institutes of Health Stroke Scale

NORSTROKE Norwegian Stroke Research Registry

OR Odds ratio

SOE Stroke of other determined etiology

SUE: Stroke of undetermined etiology

SVO Small vessel occlusion

TIA Transient ischemic attack

TOAST Trial of Org 10172 in Acute Stroke Treatment

tPA Tissue plasminogen activator

WHO World Health Organization

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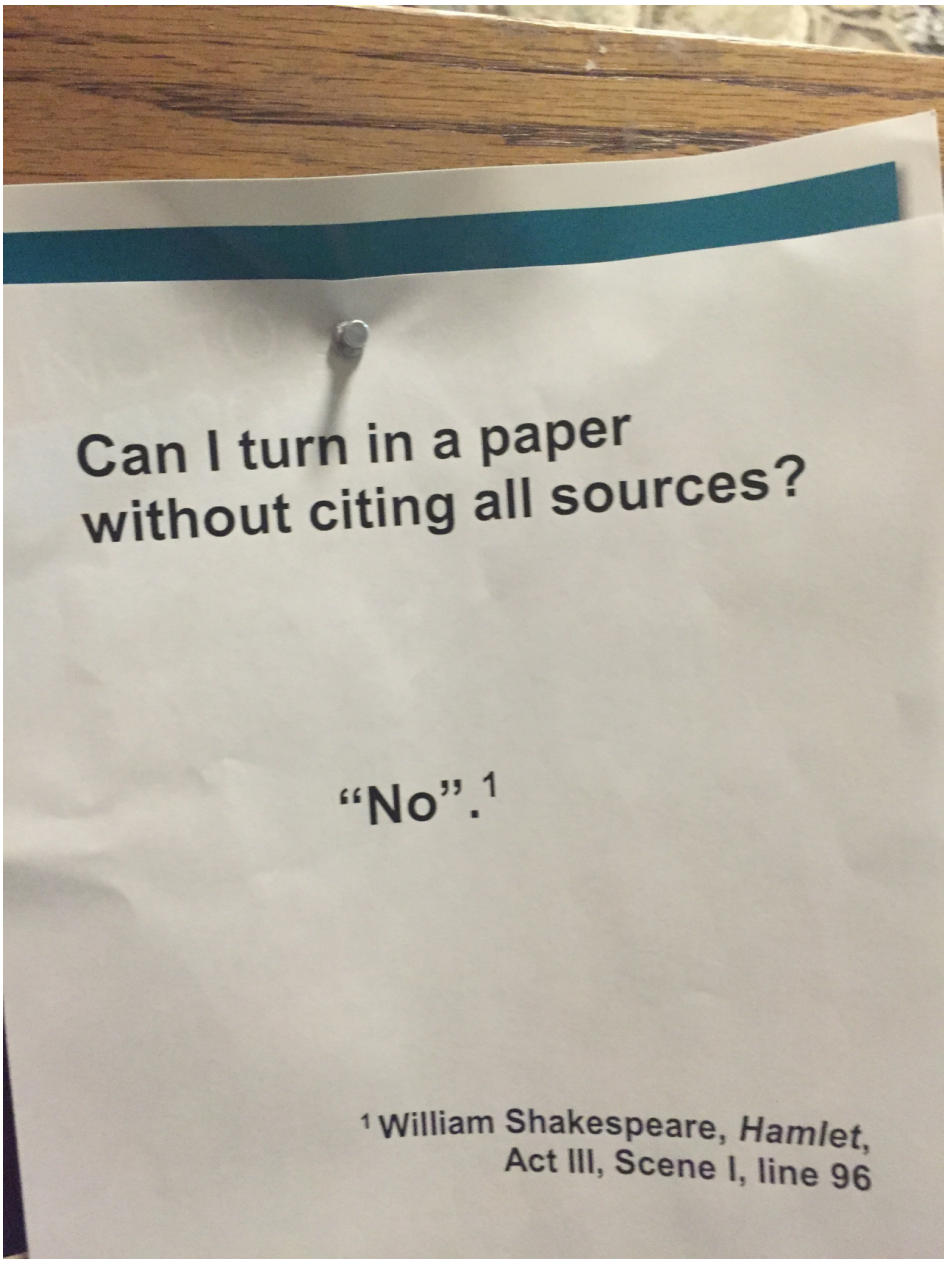
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without citing all sources?
"No".[1]
[1] William Shakespeare, *Hamlet*,
Act III, Scene I, line 96

Abstract

Ischemic stroke survivors are at high risk of experiencing new or re-expressed focal neurological symptoms. This may be due to a recurrent stroke or due to other medical conditions, known as stroke mimics. Long-term outcomes after ischemic stroke are scarcely studied. In addition, distinguishing recurrent stroke from stroke mimics is challenging. Admissions with stroke mimics are resource-consuming and may be troublesome for the patients. Knowledge on recurrence, its associated factors, mortality and stroke mimics after ischemic stroke is of value in clinical decision-making.

The present study investigated incidence, predictors and impact of recurrent stroke in a hospital-based ischemic stroke population. In addition, we investigated the burden of stroke mimics after ischemic stroke.

This thesis is based on a hospital-based cohort of patients registered in the Norwegian Stroke Research Registry (NORSTROKE) at the stroke unit at the Department of Neurology, Haukeland University Hospital. A total of 1874 surviving patients who were admitted with ischemic stroke or transient ischemic attack (TIA) between July 1, 2007, and December 31, 2013 were followed for new hospital admissions with recurrent ischemic stroke/TIA or stroke mimics.

The 30-day recurrence rate was 1.8%. Patients with large artery atherosclerosis and stroke of other etiology had increased risk of 30-day recurrence. The long-term recurrence rates were modest, being 5.4% and 11.3% at 1 and 5 years respectively. Hypertension, prior symptomatic stroke, chronic infarcts on MRI and increasing age were independently associated with long-term recurrence. Recurrence more than doubled the all-cause mortality. Stroke mimics were more common than recurrence after ischemic stroke or TIA. Stroke mimics were multi-etiological and unspecific diagnoses were most frequent directly after index stroke.

List of Publications

Paper I: **Thirty-day recurrence after ischemic stroke or TIA.**

Khanevski AN, Bjerkreim AT, Novotny V, Naess H, Thomassen L, Logallo N, Kvistad CE.

Brain and Behavior. 2018 Oct;8(10):e01108. Epub 2018 Sep 17.

Paper II: **Recurrent ischemic stroke: incidence, predictors and impact on mortality.**

Khanevski AN, Bjerkreim AT, Novotny V, Naess H, Thomassen L, Logallo N, Kvistad CE; NOR-STROKE study group.

Acta Neurol Scand. 2019 Jul;140(1):3-8. doi: 10.1111/ane.13093. Epub 2019 Apr 11.

Paper III: **Incidence and etiologies of stroke mimics after incident stroke or TIA**

Khanevski AN, Kvistad CE, Novotny V, Naess H, Thomassen L, Logallo N, Bjerkreim AT

Stroke, Stroke. 2019;50:2937–2940. DOI: 10.1161/STROKEAHA.119.026573.

Introduction

Stroke, or the ancient Hippocratic concept of "acute brain suffering", has been recognized for millennia.[2] However, the epidemiological concepts of stroke and other cardiovascular diseases have emerged merely during the last 70 years. While Keith et al. noted an association between severely elevated blood pressure and cerebrovascular disease in 1928,[3] the industrialized world was clueless about why cardiovascular disease was the main cause of death in mid-twentieth century. As U.S. President Franklin D. Roosevelt died in 1945 because of hemorrhagic stroke, the National Heart Act was created due to the incomprehension of cardiovascular causes. Subsequently, the Framingham Heart Study (FHS) was initiated.[4, 5] This epidemiological study, which is still ongoing, provided consequential insights by identificating the now established risk factors associated with coronary heart disease and cerebrovascular disease.[6, 7] Preventive strategies focusing on the identified risk factors such as smoking, hypertension and hypercholesterolemia have caused a major reduction in ischemic stroke incidence and cardiovascular mortality in industrialized countries over the last decades.[8-10] This progress means that people live longer. According to United Nations, the population aged 60 or above is increasing by 3 % each year.[11] Since ischemic stroke is endemic in people over 60, the absolute number of ischemic strokes is anticipated to rise with increasing life-expectancy, mainly due to an increase in recurrent ischemic strokes.[12]

Recurrent ischemic stroke accounts for around 30% of all strokes.[13] Still, the burden, mortality and risk factors of recurrent stroke are not sufficiently explored. In a systematic review from 2009, Norway was listed as a country with no data on stroke incidence trends.[8] In fact, the Norwegian Cardiovascular Disease Registry was established as recently as 2012.[14] Furthermore, recurrent ischemic stroke increases morbidity and mortality.[15] Rapid hospitalization with suspected recurrence represents an opportunity for reducing additional neurological deficits by effective acute interventions. However, the occurrence of new neurological symptoms in ischemic

stroke survivors may be caused by other diseases than stroke. Such conditions, labeled as stroke mimics, are unexplored in patients with prior stroke.

Current epidemiological data is valuable in order to assess temporal trends of diseases, evaluate effects of preventive measures and identify factors associated with diseases and mortality. Knowing these aspects is a valuable tool in clinical decision-making.

Ischemic stroke

Definition

Stroke, including ischemic stroke, was previously considered purely as a clinical syndrome defined by rapidly developing neurological symptoms of presumed vascular origin lasting at least an arbitrary period of 24 hours.[16] Development of diagnostic modalities and effective acute therapies of acute brain ischemia over the last decades, have led to the various tissue-based definitions. Ischemic stroke is now defined by the American Stroke Association and others as "an episode of neurological dysfunction caused by focal cerebral, spinal or retinal infarction".[17] The definition of infarction is "cell death attributable to ischemia" found by pathological studies, imaging or other objective evidence, or clinical evidence of central nervous system (CNS) ischemia lasting ≥24 hours with exclusion of other possible etiologies. This definition integrates evident vascular CNS-injury with clinical cases where current investigative methods of brain injury are inadequate or not feasible.

For this doctoral thesis, a similar definition of ischemic stroke was adopted from the Baltimore-Washington Cooperative Young Stroke Study.[18] The study defined ischemic stroke as an episode of neurologic deficit lasting >24 hours, or clinical symptoms <24 hours where magnetic resonance imaging (MRI) or computed tomography (CT) showed infarctions related to the clinical findings.

Transient ischemic attack

Definition

Clinical observations of transient and usually short-lasting neurological deficits of presumed ischemic episodes, led to the concept of transient ischemic attack (TIA) of the central nervous system. A brief episode of cerebral ischemia was thought to cause no brain damage visible by microscopy on autopsy if the patients were left with little or no deficits.[19, 20] While it was evident that the typical TIA episode was of brief

duration and usually lasting minutes, still, as for ischemic stroke, an arbitrary 24-hour definition was proposed in 1961.[19] In 1975, when this 24-hour definition was adapted by the National Institutes of Health committee, the definition of TIA was the following: "…episodes of temporary and **focal** cerebral dysfunction of vascular origin, which are variable in duration, commonly lasting from 2 to 15 minutes, but occasionally lasting as long as a day (24 hours). They leave no persistent neurological deficit."[21] The subsequent adaption of imaging techniques in the following decades changed the underlying hypothesis of TIA, as it was evident that there was poor correlation between the duration of neurological symptoms and evidence of injury of the brain tissue.[20] Several studies have demonstrated that 30% to 50% of TIAs defined by the 24-hour definition display brain injury on diffusion weighted magnetic resonance imaging (DWI-MRI).[22] Accordingly, the current definition of TIA is now tissue-based: "…focal arterial ischemia with transient symptoms (lasting <24 hours) and without evidence of infarction by pathology or imaging should be considered a TIA".[17] The same definition of TIA was used for this doctoral thesis.

Ischemic stroke incidence

Incidence is a risk estimate, or the probability of developing a disease in a population over a specified time period. Globally, there were 13.7 million new stroke cases in 2016, with large variations between countries.[9] An individual's global lifetime risk of stroke from the age of 25 years and onwards is recently estimated to be 25%, with large global variations.[23]

In 2018, there were registered 11.176 patients with ischemic stroke and 6208 patients with TIA in Norway.[24] Ischemic stroke incidence has declined substantially the last five decades in high-income countries.[8, 9] This change is also evident in the Norwegian population where the age-adjusted standardized stroke incidence rate decreased by 8.1% from 2012 to 2016, and for TIA by 13.6% in the same period.[25]

The Global Burden of Disease Study reported an 8% decline of the global- and 18.6% of the Norwegian age-standardized stroke incidence from 1990 to 2016.[9] Changes in stroke incidence is a result of changes in risk factors and stroke prevention strategies.[26, 27]

Ischemic stroke mortality

Stroke is the second leading cause of death worldwide and was responsible for 11.8% of all deaths in 2013.[28, 29] Of the 6.5 million deaths from stroke in 2013, 51% were due to ischemic stroke.[30] Assessment of ischemic stroke mortality is complex due to inclusion of hemorrhagic stroke in many epidemiological studies on mortality, as well as the use of different mortality measures (e.g. cause-specific mortality vs all-cause mortality) across studies. Up to 75% of all deaths within the first year after stroke occur during the first three months, but inclusion of intracerebral hemorrhages in these studies inflates early mortality.[31-35]

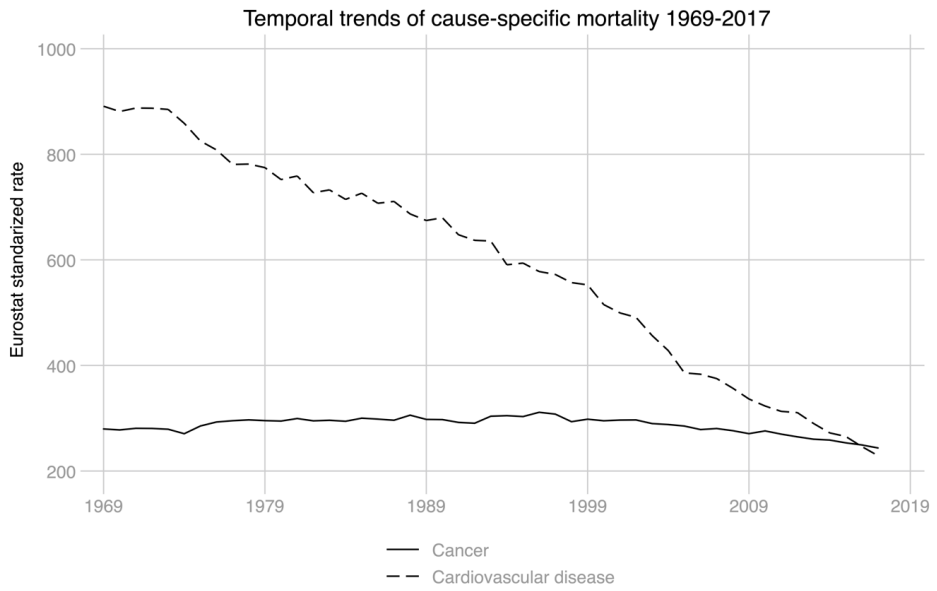
Early case fatality rate

The early case fatality rate is the proportion of patients that die shortly after an event, in this case ischemic stroke, regardless of the death cause. The time period after the event to early death is usually defined as up to 28-30 days.[9, 36] Early case fatality after ischemic stroke ranged from 13–23% in high-income countries between the years 2000 and 2008.[8] Early case fatality after ischemic stroke declined by about 1% per year in high -income countries between the years 1970 and 2008, although with varying estimates across populations.[37]

Cause-specific mortality

The clinical and neurological consequences of ischemic stroke are directly associated with mortality during the first week after stroke onset.[38, 39] Mortality after the first week is largely due to complications of stroke, like infections, venous thromboembolism or other systemic medical complications.[29, 37, 40] In 2016 in Norway, a total of 1927 people died due to a stroke; 401 of which were ischemic, 446 hemorrhagic and 1080 unspecified.[25] Cause-specific mortality after ischemic stroke has declined substantially over the last decades.[29, 37, 40] This is clearly evident in the Norwegian population, where the age-standardized stroke mortality rate declined by 25% just from 2012 to 2016.[25]. While cardiovascular diseases were responsible for more than half of all deaths in Norway in the 1960s and -70s, this proportion was halved in 2017.[41] And for the first time, cancer was the leading cause of death in Norway in 2017 (Figure 1).[41]

Figure 1



Long-term mortality

Ischemic stroke patients have increased long-term mortality compared to stroke-free individuals.[42, 43] Functional status in stroke survivors is a strong predictor of long-term mortality.[44] In a Norwegian study, 86.5% of stroke patients had died during the 12-year follow-up period.[45] Studies on long-term mortality after ischemic stroke are scarce. In addition, differences in study design and populations makes evaluation of long-term mortality difficult.

Etiology and classification of ischemic stroke and TIA

Brain ischemia is considered to have three main etiologies: thrombosis, embolism or hypoperfusion.[46] The common denominator for thrombosis and embolism in an arterial occlusion leading to focal ischemia in a region of the brain. In thrombosis, blood flow to a region of the brain is inhibited due to a local process causing obstruction within the vessel. In embolism, blood flow is inhibited due to a thromboembolic clot originating somewhere else in the circulation. In hypoperfusion, brain ischemia is caused by a reduction of cerebral perfusion pressure below a critical threshold, and ischemia usually develops first in the border zones between the major cerebral arteries.

Determination of the etiology of the ischemic event is essential, as etiology impacts treatment and outcome after ischemic stroke.[47] Hence, the three above described main etiologies are further divided into subtypes, as the risk of recurrence and outcomes differ based on the location and type of the ischemic process. In the case of thrombosis, there is a significant difference in risk of recurrence if the atherosclerotic process originates in a large (e.g. carotid) or a small (e.g. lenticulostriate) vessel. In the case of embolism, treatment is dependent on the origin of the emboli (e.g. heart or the venous system). These observations have led to development of different classification systems. The Trial of Org 10172 in Acute Stroke Treatment (TOAST),

which was used in the present study, is an etiological classification system originally developed for clinical trial standardization, but is now routinely applied in clinical practice.[48] TOAST classifies stroke into five subtypes: large-artery atherosclerosis (LAA), cardio embolism (CE), small vessel occlusion (SVO), stroke of other determined etiology (SOE), or stroke of undetermined etiology (SUE). Classification of an ischemic stroke or TIA into one of these subtypes is based on a combination of clinical features and diagnostic tests such as brain imaging, cardiac examinations (echocardiogram, ultrasound, etc.), imaging of extra- and intracranial vessels, and laboratory tests.[49] While TOAST may be the most adopted classification system, it has also been criticized because a high proportion of patients, in many studies up to 40%, are classified into the unspecific "stroke of undetermined etiology" category.[50, 51] This is in part due to a nonhierarchical classification structure where strokes with several possible etiologies are grouped into SUE. In an attempt to improve precision, several other classification systems have been developed. The most frequently used are ASCO (A for atherosclerosis, S for small-vessel disease, C for cardiac source, and O for other cause), SSS-TOAST (Stop Stroke Study Trial of Org 10172 in acute stroke treatment), CCS (Causative Classification System) and CISS (Chinese ischemic stroke subclassification).[52-55] They all differ in their reliability to classify strokes into subtypes, which makes comparison between them challenging.[53, 56, 57] Classification systems also suffer from inter-observer variability, which is especially evident in studies with small sample sizes.[58] Although one study found that CCS had higher validity and generated better distinct subtypes compared with TOAST and ASCO,[51] TOAST still seem to remain the most used system.

TOAST subtypes

Large-artery atherosclerosis (LAA): Atherosclerosis is a process originating in the tunica intima layer of arteries in regions of disturbed blood flow. The cause is dysfunction of the endothelial cells that triggers an inflammatory response and

triggers retention of lipoproteins in the subendothelium.[59] This process usually develops in sites where arteries branch, bifurcate or curve, due to high shear stress-gradients (atheroprone flow).[60] These depositions of lipids cause plaques, which may rupture and cause local obstructions of arteries, or releasing emboli causing distal occlusions. Large arteries include both the extracranial arteries (carotids and vertebral arteries) and proximal branches of the intracranial arteries, including the Circulus Willisi. LAA is one the most common stroke subtypes, causing about 10-30% of all strokes depending on the age and ethnicity of the population.[61-70] There are also major geographical differences in prevalence of intracranial atherosclerotic disease (ICAD), which is especially prevalent in Asia.[71] TOAST criteria require an intra- or extracranial stenosis of >50% to classify a stroke as LAA, a criterion originating from the NASCET study in which carotid stenoses were graded from angiograms.[49] Since then growing evidence has shown that even in non-stenotic arteries, both intra- and extracranial, the presence of high-risk atherosclerotic plaques may cause ischemic stroke or TIA due to artery-to-artery embolization.[72, 73]

Cardioembolism (CE): An emboli from the heart to the brain can result from three mechanisms: local hemostasis (e.g. ventricular aneurysm), release of material from an abnormal valvular surface, or paradoxical (venous) emboli.[74] Essentially any heart condition can lead to formation of an embolus, but the most frequent cardiac condition associated with CE is atrial fibrillation (AF). Other causes of cardioembolic stroke are systolic heart failure, recent myocardial infarction, patent foramen ovale, aortic arch atheroma, prosthetic heart valves and infective endocarditis.[75] CE causes in general more severe strokes than other subtypes with worse outcome and higher socio-economic costs.[76-79] CE is responsible for about 20% of all ischemic strokes.[80]

Small vessel occlusion (SVO): Cerebral small vessel disease (SVD) is a term used to describe different pathological processes affecting small arteries, arterioles, venules and capillaries of the brain.[81] SVD shares some common characteristics with large artery disease, like endothelial dysfunction and inflammation, but has also its unique features due to different vascular structure and mechanics.[82] The resulting vascular damage, termed arteriosclerosis, lipohyalinosis or fibrinoid necrosis, is characterized

by fibrin deposition and smooth muscle damage, resulting in a thickened and stiff vessel wall.[83] These processes may lead to local vessel occlusion, although there are indications that distal embolization from other vessels may also occur.[84] The resulting lesions are mainly located subcortically and are observed as lacunar infarcts, microbleeds, white matter intensities or even large hemorrhages. SVD is also an established cause of cognitive impairment, most likely due to disruption of functional networks in the brain.[85, 86] The proportion of ischemic stroke caused by SVO ranges from 7-40% in different populations.[66-70]

Stroke of other determined etiology (SOE): Beside cardiovascular disease, there are a large number of traumatic, immune-mediated, genetic, hematological, infectious, malign and other causes of stroke.[80] One of the most common causes is dissection of extra- or intracranial arteries.[87, 88] SOE is especially prevalent in young stroke patients, where it accounts for 20-30% of cases.[89, 90]

Stroke of undetermined etiology (SUE): Often, and even with thorough evaluation, the etiology of a stroke is not found. Stroke etiology is classified as SUE when an apparent cause is lacking. This may occur either despite proper examinations, or when multiple competing etiologies are identified, or due to insufficient examinations, like with the concept of embolic stroke of undetermined cause (ESUS).[48, 91] When stroke etiology is classified by TOAST, up to 50% of patients will end up with an undetermined or cryptogenic cause.[50, 51]

Ischemic stroke risk factors

There are many risk factors associated with ischemic stroke. As for other diseases, by nature, some are modifiable, and some are not. Non-modifiable risk factors are factors that influence the risk and etiology of stroke, but are not alterable. Example of such factors are age, sex, race/ethnicity and genes (currently).[92] Modifiable risk

factors are conditional on a patient's environment and subject to change by will or treatment. Example of such factors are comorbidities and lifestyle choices (e.g. smoking, diet, alcohol consumption, amount of physical exercise). A study with 26919 participants from 32 countries worldwide reported that 90% of stroke risk was attributed to ten modifiable risk factors: hypertension, current smoking, waist-to-hip-ratio, diet, physical activity, diabetes mellitus, alcohol intake, psychosocial factors, cardiac disease and ApoB/ApoA1 ratio.[93]

Age

The incidence of stroke increases with age and affects mainly people aged 60 years and older.[10] In a meta-analysis including studies worldwide, mean age for first stroke was 68.6 years for men and 72.9 for women.[94] For the Norwegian population, the mean age for first stroke in 2017 was 72 years and 77 years for men and women respectively.[95] As previously mentioned, a population-wide reduction in ischemic stroke incidence in industrialized countries has been observed over the last decades.[8, 9] This applies mainly to the elderly population (>54 years of age) as a significant increase in incidence has been observed in the young.[96] It is unclear if this increase in young stroke is due to changes in risk factors among the younger population, or advances in stroke diagnostics driven by a substantially increased use of MRI.

Sex

A meta-analysis reported that males have a 33% higher stroke incidence rate than females, although females have a 41% higher prevalence of stroke.[94] The latter is due to longer life expectancy in women.[97] Some stroke risk factors are unique for females, such as different composition of sex hormones, estrogen intake and factors associated with pregnancy and the post-partum state.[98] Because of these sex-specific factors, women have a higher stroke risk at younger age than men.[99]

Race/ethnicity

There are significant ethnic differences in stroke risk. The prevalence and burden of common stroke risk factors differ substantially between races.[93, 100-104] For instance, blacks have in general more vascular risk factors than Caucasians and the proportion of intracranial atherosclerosis is higher in Asians.[72, 104] Although some of the observed ethnic disparities may be ascribed to differences in health-care access, awareness about these differences is important in a world with considerable human migration.[99]

Genetic factors

The risk of ischemic stroke is influenced by hereditary factors. Both single genes and genome wide genetic variants have been associated with increased stroke risk.[99, 105] A study that assessed heritability of ischemic stroke from genome wide association studies data (GWAS) found that heritability for all types of ischemic stroke was 37.9%, but varied significantly between subtypes. The highest heritability was reported for LAA whilst the lowest was reported for SVO.[106]

Hypertension

Hypertension is a highly prevalent modifiable risk factor for ischemic stroke.[82, 107, 108] Hypertension is now defined as systolic BP ≥130 mm Hg and/or diastolic BP ≥80 mm Hg.[109] The risk of stroke is increasing with increasing blood pressure levels, also in patients with pre-hypertension (systolic BP 120-129 mm Hg).[110, 111] Conversely, treating hypertension has a significant effect on stroke risk. A Norwegian study found that lowering of systolic blood pressure accounted for 26% of the observed 1.7% annual decline of ischemic stroke incidence in the Tromsø area.[27] In 2017 in Norway, 57% of patients with stroke were on antihypertensive drugs prior to the stroke.[95]

Dyslipidemia

Elevated cholesterol is one of the major factors in the development of atherosclerosis and ultimately cardiovascular disease.[10, 112] This is especially relevant to coronary heart disease where atherosclerosis is a key element.[113] Stroke is a much more heterogeneous disease and the relationship between stroke and lipids is more complex. Elevated total cholesterol levels are associated with ischemic stroke of LAA and SVO subtypes.[114]

Diabetes mellitus

Hyperglycemia manifested as diabetes mellitus, as well as prediabetes, is a major and increasingly prevalent risk factor of ischemic stroke.[115, 116] Diabetes doubles the total risk of having an ischemic stroke and is associated with poorer outcomes.[115, 117]. The duration of the disease is also significant. One study found that the risk of ischemic stroke increased 3% each year with diabetes.[118] In some studies, the prevalence of prediabetes is as high as 50% in ischemic stroke patients.[116] In Norway, the prevalence of known or concurrent diabetes among stroke patients was 18.2% in 2017.[95]

Atrial cardiopathy and atrial fibrillation

Atrial fibrillation (AF) is in numerous studies persistently associated with increasing the risk of ischemic stroke. Cardioembolic ischemic stroke is increasing in high-income countries due to higher life expectancy, increasing prevalence of AF and better control of risk factors leading to LAA and SVO strokes.[119, 120] In a recent publication from the Oxford Vascular Study (OXVASC), one of three incident ischemic strokes were associated with AF.[121] AF is considered to increase the risk of stroke 3-to 5-fold and affects at least 9% of all people aged 80 years and older.[122, 123]

Recent findings have questioned the long-lived assumption that AF is an essential thrombogenic component in Virchow's triad and the direct cause of atrial blood stasis in thrombus formation.[124, 125] In a study from Taiwan, AF did not increase the risk of stroke in men without other risk factors (CHA_2DS_2-VASc score = 0).[126] In several studies, continuous heart rate monitoring detected AF only after incident stroke, despite monitoring several months prior to the stroke.[127, 128] Other types of atrial disease (e.g. premature atrial contractions) without evidence of AF or other tachyarrhythmias have also been associated with increased risk of embolic stroke.[99, 129] This evidence has led to the concept of atrial cardiopathy, a term that also includes other pathological processes in the left atrium besides AF as cause of cardioembolic stroke.[130]

Lifestyle factors

Smoking, both active and passive, is unfortunately still a major risk factor for stroke. Current smoking doubles the risk of stroke with a dose-dependent effect, as the risk increases with 12% for each increment of 5 cigarettes/day.[131] Other life-style factors associated with increased risk of stroke are sedentary behavior, nutritional factors and obesity.[99] While heavy alcohol consumption is a risk factor for ischemic stroke, moderate alcohol consumption (≤14 units/week for men and ≤7 for women) is thought to be protective.[132] Recent studies have questioned this association demonstrating an increase in stroke risk even with light alcohol consumption.[133]

Stroke triggers

Observations of patterns in the onset of ischemic stroke in relation to different acute factors, has led to evolution of the concept of "stroke triggers".[134] These factors transiently increase the risk of stroke and may be related to other diseases, the environment or a patient's behavior. Examples of such triggers of ischemic stroke are

drug/alcohol abuse, infection/sepsis, stress, air pollution and changes in the ambient temperature.[134-140]

Ischemic stroke prevention

The goal of stroke prevention is reduction of stroke incidence by risk factor modification. High-quality prevention of ischemic stroke has the potential of reducing both the absolute number and the severity of strokes, with a reduction in suffering and costs involved in salvaging and rehabilitating established disease.[108] In general, prevention may be achieved on three different levels; 1) primordial prevention, which is prevention of risk factor development on a group level;[141] 2) primary prevention, which is modification and improvement of risk factors of ischemic stroke on an individual level once present;[142] and 3) secondary prevention, which is prevention of ischemic stroke recurrence in a patient who has suffered a stroke.[13]

Primordial prevention

Primordial prevention is ultimately risk reduction through behavioral modification in a population, such as increase in physical activity, smoking cessation strategies and elimination of public passive smoking exposure, promotion of healthy diets, diet sodium reduction and diabetes screening.[143] Clinical studies on the effects of a "polypill", containing a fixed dose combination of blood pressure agents and a statin (with or without acetylsalicylic acid), in middle-aged individuals without cardiovascular disease, demonstrate potential for major risk reduction on a population level.[144, 145] Such strategies may be especially attractive in countries where access to health care is limited.

Primary prevention

Addressing major risk factors for cardiovascular disease in an individual is the cornerstone of primary prevention. Intuitively estimating an individual's risk of future cardiovascular events or death is difficult, because cardiovascular risk is conditional on many factors. Thus, several scoring systems have been developed for different populations, such as the Framingham Risk Score, SCORE, ASCVD Risk estimator + and NORRISK2.[142, 146-148] These risk estimators typically calculate an individual's 10-year risk of a cardiovascular event or death based on factors like age, sex, blood pressure levels, cholesterol levels, diabetes and smoking. Risk estimation is a valuable asset in order to determine the measures, timing and treatment goals of primary prevention in risk patients.[142] A French study demonstrated that general practitioners intuitively rated the cardiovascular risk incorrectly in >70% of patients, rated as high-risk by the Framingham and SCORE systems.[149]

Secondary prevention

In patients with established ischemic stroke or TIA, the main intention of diagnostic evaluation is to initiate the most appropriate measures to reduce the risk of further strokes. Improved acute stroke treatment with higher rates of thrombolytic- and endovascular treatment, more independence and improved survival, indicates that an increased number of stroke survivors are susceptible to recurrent strokes.[8, 29, 150-153] Secondary prevention focuses on identification of stroke etiology, administration of proper preventive treatment (e.g. medications, carotid revascularization) and modification of cardiovascular risk factors (e.g. exercise, smoking cessation, dietary changes).

Almost all ischemic stroke patients are treated with some type of antithrombotic therapy, either antiplatelet or anticoagulant therapy. Antiplatelet agents reduce the risk of recurrence in non-CE stroke patients by about 15%,[154] while anticoagulants

lower the ischemic stroke risk by about 60% in patients with atrial fibrillation.[155] Anticoagulants are recommended as secondary prevention therapy in most patients with CE-stroke[156] and are in general not indicated in non-CE stroke due to their association with major hemorrhage, which outweighs their efficacy in preventing recurrence in other subtypes than CE.[157]

In addition to antithrombotics, treatment of hypertension may be the most significant measure.[156] About 60-70% of stroke patients have a history of, or present hypertension at the index event.[158-161] Many large randomized controlled trials have demonstrated an association between blood pressure reduction and reduced risk of recurrent stroke. A recent meta-analysis of such studies found a 27% risk reduction of recurrent stroke with antihypertensive treatment, and this association was linear with decreasing levels of systolic and diastolic pressure.[162]

Statin therapy is also a main component of non-CE secondary ischemic stroke prevention, although the association between cholesterol levels and ischemic stroke risk is more uncertain.[156] Meta-analyses have demonstrated a 16% reduced risk of recurrent stroke of with statin therapy,[163, 164] but there are indications that this effect is due to the anti-atherothrombotic effects of statins and not due to the reduction of blood cholesterol levels.[165]

Optimal combination of secondary prevention therapies is necessary for maximum risk reduction of recurrence and death. In a multicenter study from Korea, optimal therapy reduced the risk of recurrent stroke with 60%, risk of major vascular events with 61% and all-cause mortality with 65%, compared with no secondary prevention therapy.[26] In addition, a study reported that discontinuation of acetylsalicylic acid was associated with a 40% risk increase of recurrent ischemic stroke or TIA compared with continuation of therapy.[166] The effects of different secondary prevention medications are additive.[167]

Recurrent ischemic stroke

Recurrent ischemic stroke accounts for 25-30% of all strokes and increases morbidity and mortality in stroke patients.[13, 15] The risk of recurrence is highest directly after incident ischemic stroke or TIA and declines over time.[168] Many large incidence studies on recurrent stroke have excluded events occurring within the first month, meaning that data regarding early recurrence is limited and variable in quality.[169] Studies have reported recurrence risks of 1.6-15% at 30 days, 2.3-18% at 90 days, 5.1-20.6% at 1 year and 16.2-38.7% at 5 years.[15, 34, 36, 159-161, 168, 170-194] A meta-analysis reported a cumulative risk of stroke recurrence of 3.1% at 30 days, 11.1% at 1 year and 26.4% at 5 years.[168]

The risk of ischemic stroke after TIA was previously considered to be high, especially the first few days. Several studies conducted around the year 2000 reported an ischemic stroke risk of around 10% the first month after clinical TIA, where up to half of recurrences happened during the first couple of days.[195-197] Increasingly urgent management of TIA over the last decades have led to lower rates of ischemic stroke after TIA in recent studies, estimated to 2.8%, 5.1% and 9.5% at 30 days, 1 year and 5 years respectively.[174, 198]

The risk of undergoing a cerebral hemorrhage as the first recurrent event is low. Several studies have reported that in patients with ischemic stroke, the risk of the recurrent event being an intracerebral hemorrhage is about 5%.[187, 199] This risk of intracerebral hemorrhage as recurrent event changes to 58% if the initial event was an intracerebral hemorrhage.[199]

The association between risk of recurrent ischemic stroke and index stroke subtype is uncertain. This uncertainty is in part due to differences between studies regarding populations, etiology classification and statistical methods. Some studies found an association between risk of recurrence and subtype, reporting the highest association for large-vessel disease and cardioembolic stroke.[185, 200-202] Other studies did not find

any association between subtype and risk of recurrence.[34, 68, 160, 203, 204] Stroke due to large artery atherosclerosis has been consistently associated both with early recurrence and with recurrence in younger patients.[67, 161, 171, 200, 205, 206]

Recurrent stroke risk factors

Many risk factors have been associated with recurrent stroke, even though there is a lack of consistency across studies. While recurrent ischemic stroke also is strongly associated with the major cardiovascular risk factors, no single factor has been consistently associated with recurrent ischemic stroke or TIA.[207] Hypertension, level of education, prior stroke, diabetes, coronary heart disease, silent brain infarction, alcohol abuse, persistent smoking, discontinuation of aspirin, atrial fibrillation and the total burden of risk factors have all been reported as significant risk factors for recurrent stroke in different studies.[160, 166, 173, 186, 194, 202, 203, 207-217]

Recurrent ischemic stroke and mortality

Few studies have assessed the effect of recurrent ischemic stroke on mortality. A study from The Northern Manhattan Stroke Study did not find any difference in mortality between ischemic stroke patients with and without prior stroke.[194] Another study on 50.000 Medicare patients reported that patients with recurrent stroke had poorer 2-year survival compared to patients with first stroke.[182] Other studies have reported estimates ranging from a two-fold to a 17-fold increase in mortality after recurrence.[15, 217-219] In these studies, recurrence has in general been the strongest factor associated with mortality.

Stroke mimics after incident stroke

Acute neurological symptoms may be non-specific or caused by other diseases than stroke. Consequently, many patients with suspected stroke turn out to have other

conditions, which are labeled as stroke mimics. A stroke mimic is usually defined as a condition not resulting from cerebral ischemia, but still presenting itself with neurological symptoms indistinguishable from stroke.[220] Conditions like infections, migraine, seizures, syncope, vertigo, confusional states and functional symptoms are frequent stroke mimics.[221-224] Stroke mimics lead to costly hospital admissions and are stressful for the patients and their family.[225] Recognition of stroke mimics is therefore highly important, especially in an era with constant focus on shortening the time from hospital admission to administration of thrombolysis (door-to-needle time).

While stroke mimics in patients without prior stroke have been subject of numerous studies,[220-223, 226, 227] the phenomenon of stroke mimics is unexplored in patients with prior stroke. A brain already impaired from stroke is more likely affected by altered metabolic processes due to infections, seizures or other diseases, which may cause post-stroke recrudescence (PSR) of prior deficits.[228] A recent study from the U.S. demonstrated that a history of prior stroke increased the risk of misdiagnosing a recurrent stroke more than two-fold.[229] Thus, information about incidence and types of stroke mimics after ischemic stroke may be of benefit to clinicians in decision-making.

Aims of the thesis

1. To assess short- and long-term incidence of recurrence after index ischemic stroke or TIA (Paper I and II).
2. To determine the etiologies of short-term recurrence (Paper I).
3. To assess factors associated with short- and long-term recurrence after ischemic stroke or TIA (Paper I and II).
4. To assess the incidence of all-cause mortality after index ischemic stroke or TIA (Paper II).
5. To assess the impact of recurrence on all-cause mortality after index ischemic stroke or TIA. (Paper II)
6. To assess the cumulative incidence of stroke mimics after index ischemic stroke or TIA and compare it to the incidence of recurrent ischemic stroke or TIA in the same time-period within the same population. (Paper III)
7. To assess etiologies of stroke mimics after index ischemic stroke or TIA and investigate if these etiologies varies in frequency based on elapsed time after index ischemic stroke or TIA. (Paper III)

Materials and methods

This thesis investigates recurrent events in a hospital-based prospective cohort from the Stroke Unit at the Department of Neurology, Haukeland University Hospital, Bergen, Norway. All papers in the present thesis are based on index admission patient data from the NOR-STROKE registry, with subsequent follow-up data acquisition from the included patient's electronic medical journals. The thesis is based on patients registered in the NOR-STROKE registry with index ischemic stroke or TIA between June 2007 and December 2013. Patients were followed for recurrent events from discharge and until September 1, 2016. Follow-up data collection was performed mainly during 2017.

The study population is identical in all papers. During the inclusion period, 1988 patients were diagnosed with ischemic stroke or TIA in the Stroke Unit, of whom 116 died during the index admission or were discharged to palliative care (5.8%). The final cohort consisted of 1872 patients with index ischemic stroke (n = 1666) or TIA (n = 206). In paper I, the studied cohort consisted of 1874 patients. During data analysis for paper II and III, two patients were found to be misclassified in the NOR-STROKE registry as they had ICH as the index event. This was probably due to a registry plotting error and these patients were excluded from the analyses in paper II and III.

Data from the index stroke admission

The NOR-STROKE registry is an ongoing, prospective hospital-based registry that has included stroke patients admitted to the stroke unit at Haukeland University Hospital since 2006. The registry is a medical quality registry and is approved by the regional ethics committee and The Norwegian Data Protection Authority. Approximately 275 000 people are living in the area served by this stroke unit. The

stroke unit is the primary unit for all stroke patients geographically affiliated with Haukeland University Hospital, as well as stroke patients <60 years of age that are affiliated with a neighboring hospital (Haraldsplass). For this thesis, only patients that lived inside this area at the time of the index ischemic stroke or TIA and were geographically affiliated with the Haukeland University Hospital stroke unit were included. Patients who moved outside of the defined geographic area before the end of data collection, and patients that died during index admission or were discharged to palliative care, were excluded from the study. Patients geographically affiliated with Haukeland University Hospital Stroke Unit, but admitted to other hospitals with index stroke, were also excluded from this study.

Admission of patients with suspected stroke to Haukeland University Hospital happened either through primary care physicians (general practice or out-of-hours services), or directly to the hospital through the "code stroke" pathway, defined by the emergency medical dispatch protocol as suspected stroke with symptom onset <6 hours. The National Institute of Health Stroke Scale (NIHSS) score was registered at admission. Computed tomography (CT) was performed in all patients without wake-up stroke to exclude intracranial hemorrhages, assess early ischemic changes, or other symptomatic pathologies. In order to detect occlusions accessible to endovascular treatment, CT angiography was performed in patients with symptom duration <6 hours. Patients with wake-up stroke were assessed with MRI DWI upon availability. The use of CT angiography, wake-up MRI and MRI in TIA patients evolved during the inclusion period. Thrombectomy was available as an experimental procedure from 2008, with an increasing number of thrombectomies over following years.

Routine examinations of stroke patients in the stroke unit included brain imaging with MRI, duplex carotid ultrasound, ECG, 24-hour minimum electrocardiographic monitoring, echocardiography if indicated and laboratory analyses. MRI was performed at index in a total of 87% (1629/1872) of patients in the cohort: in 88% (1465/1666) of patients with ischemic stroke and in 80% (164/206) of patients with TIA. Indications for assessment of dysphagia, apraxia and cognitive function by a speech therapist or occupational therapist were liberal.

The treating stroke neurologist administered NOR-STROKE registry inclusion during admission. Registration of data was conducted by use of a standardized form, which was filled in by the neurologist during stroke admission. The form included basic patient and clinical data like date and time of symptom onset, duration of symptoms, all registered NIHSS scores, functional scores and status, vital parameters, imaging data, results of diagnostic test, complications, prior medial history, cardiovascular risk factors, medications at admission/discharge and discharge status and destination. The patient was interviewed about the specific parameters during the index admission. Presence of comorbidities like hypertension, previous ischemic stroke or TIA or other cardiovascular disease were based on information from direct questioning, on existing hospital medical records, or if the patient were already on medications for specific conditions upon admission. In addition to the self-reported information from the patient, data from complementary sources like family (spouse, children, and other relatives) were also gathered when necessary. The current version of the pages in mention from the NORSTROKE form is included in the Appendix.

Hypertension was defined as a history of treated hypertension or if the patient were using antihypertensive medications for hypertension upon index admission. Diabetes mellitus was defined as use of antidiabetic medication upon index admission. Hypercholesterolemia was defined as the use of lipid-lowering drugs upon index admission. Peripheral artery disease (PAD) was defined as a history of diagnosed peripheral artery disease prior to index admission.

Prior ischemic stroke or TIA were defined as a history of a clinical episode of ischemic stroke or TIA reported by the patient or based on available medical journal information at index admission.

Written informed consent to participate in the registry was obtained during admission from all patients or their legally authorized representatives if possible.

Follow-up data

Follow up data was obtained by accessing electronical hospital medical records. Recurrent events after index discharge were identified by identification of all new acute hospital admissions in the study period by looking up electronic medical records from all ten hospitals in the region administered by the Western Norway Regional Health Authority. The included hospitals are Haukeland University Hospital, Haraldsplass Deaconess Hospital, Voss Hospital, Stord Hospital, Odda Hospital, Haugesund Hospital, Førde Central Hospital, Nordfjord Hospital, Lærdal Hospital and Stavanger University Hospital. The region is one of four regional health authorities in Norway including approx. 1.1 million inhabitants in Western Norway.

Every Norwegian citizen has a unique 11-digit national identity number which is given for life. This number is used for most administrative purposes, such as hospital admissions. All hospital records in Western Norway dating back several decades are electronic and are easily accessed for these patients with the national identity number.

Data collected for each acute new admission included the dates for admission and discharge, primary and secondary admission departments, primary and secondary diagnosis (ICD-10, International Classification of Diseases, Tenth Revision), vital parameters, current smoking, if the admission was due to suspected stroke and also discharge destination. All new acute admissions with a diagnosis of ischemic stroke, TIA or stroke mimics were used for the analyses. For identification of stroke mimics, we tagged all acute admissions where the admission report diagnosis was suspected stroke, but the primary discharge diagnosis was other than ischemic or hemorrhagic stroke, or TIA. Suspected stroke was defined as a diagnosis of possible stroke in the admission report, or stroke investigation in patients admitted through the "code stroke" pathway where suspected stroke was the dispatch diagnosis by the emergency medical dispatch protocol.[230] Current prescribed medications for each patient were registered at the first and last admission after index discharge. The primary ICD-10 discharge diagnosis was registered. Stroke mimic was defined as any ICD-10 discharge diagnosis other than intra-axial cerebral hemorrhage (ICH) (I61), ischemic

stroke (I63) or TIA (G45, excluding transient global amnesia G45.4). Cases with extra-axial hematomas, traumatic ICH and ICH related to neoplasia or thrombolytic treatment were excluded from the analysis.

Information on death was collected electronically from the Norwegian National Registry through the medical electronic records system, DIPS, which is used by all ten hospitals administered by the Western Norway Regional Health Authority. Date of death were registered during the data collection phase in 2017. Elective admissions were not included in the present study.

The collected data was categorized in a standardized form, created and stored in a data entry and documentation computer program (EpiData 3.1, Odense, Denmark).[231]

For all papers included in the thesis, definition of recurrent ischemic stroke or TIA was the same as for the index stroke event, as described previously. Intracerebral hemorrhage or subarachnoid hemorrhage were not included as recurrent cerebrovascular events, as these conditions differ in pathology and are often associated with preventive medications prescribed after ischemic stroke or TIA.

In paper I, the aim was to assess the etiologies of recurrent stroke the first 30 days after the index event. A secondary review of electronic medical charts focused on revision of the etiological evaluation, review of supplemental clinical and imaging data, with emphasis on intracranial pathology. Two doctors with experience in stroke medicine (ANK and HN) performed this review. A common cause for both episodes was reviewed and determined if possible.

In paper II, the aim was to estimate the long-term cumulative incidence of recurrent ischemic stroke or TIA. We also determined the factors associated with long-term recurrence and how recurrent stroke influenced the all-cause mortality.

In paper III, the aim was to estimate the long-term cumulative incidence of stroke mimics after incident ischemic stroke or TIA and compare it to the cumulative

incidence of recurrent ischemic stroke or TIA within the same population in the same time period. Only admissions where clinical testing and observation in a stroke unit for possible stroke was initiated after initial emergency room evaluation were included in the analysis.

Statistics

Univariate analyses were performed using the chi-squared test for categorical variables, and Students' *t*-test for continuous variables. Wilcoxon rank-sum test was used for skewed continuous variables.

Backward stepwise Cox regression was used for the multivariate analyses by inclusion of variables that turned out significant ($P<0.05$) in the univariate analyses. All models included age, sex, and functional scores (mRS/NIHSS) from index admission for confounding adjustment.

Cumulative incidence of recurrence and stroke mimics was calculated with the cumulative incidence function (CIF) in a Cox model after applying the method of Fine and Gray by treating death as a competing risk.[232] The Kaplan-Meier method was used to estimate the incidence of all-cause mortality.

A Cox regression model with recurrence as a time-dependent covariate was constructed to assess the effect of recurrence on all-cause mortality in paper II. Known factors associated with mortality such as age, smoking, stroke severity and cardiovascular risk factors for stroke were included in the model.

Visual inspection of the proportionality hazards-assumption showed no violation of proportionality in the models.

In assessment of incidence rates, we accounted for the fact that some patients had several events of recurrent ischemic stroke or TIA (paper II) or stroke mimics (paper III) by creating an Andersen-Gill regression model.[233] This model, which is an extension of the Cox model, is a method for analyzing data with repeated events. This is in contrast to the regular Cox model, which censors observations after occurrence of an event in question. The incidence rates per 1000 years with Poisson confidence intervals were calculated from the number of total failures divided by the person-time.

Analyses were performed by use of Stata/SE 15.1 (Stata Corp LLC, LP, TX).

Summary of results

Paper I: Thirty-day recurrence after ischemic stroke or TIA

We identified 1874 patients who were discharged alive from our stroke unit after their index ischemic stroke or TIA during the inclusion period. A total of 33 patients, 28 with ischemic stroke and five with TIA, (1.8%) were readmitted within 30 days after index stroke onset. By using TOAST, 12 patients were initially classified with stroke of unknown etiology (SUE). Etiologies behind recurrent ischemic stroke or TIA were after review of the recurrent episode identified as extracranial large artery atherosclerosis (LAA) in 14 patients (42.4%), intracranial arterial pathology in seven patients (21.2%), stroke of other etiology (SOE) in six patients (18.2%) (particularly active malignancy), and Cardioembolism (CE) in four patients (12.1%). Small vessel occlusion (SVO) and SUE were the causes in one patient each. Logistic regression showed that patients with stroke of other determined etiology (SOE) and LAA had increased risk of 30-day recurrence (OR = 9.72, 95% CI 1.84–51.3, $p < 0.01$ and OR = 4.36, 95% CI 2.01–9.47, $p < 0.01$, respectively).

Patients with LAA and SOE had increased risk of recurrent ischemic stroke or TIA within 30 days.

Paper II: Recurrent ischemic stroke: Incidence, predictors, and impact on mortality

We identified 1872 patients who were discharged alive from our stroke unit after their index ischemic stroke or TIA during the inclusion period. During follow-up, 220 patients had 277 recurrent ischemic strokes or TIAs. The cumulative recurrence rate was 5.4% at 1 year, 11.3% at 5 years, and 14.2% at the end of follow-up. Hypertension (HR = 1.65, 95% CI 1.21-2.25), prior symptomatic stroke (HR = 1.63,

95% CI 1.18-2.24), chronic infarcts on MRI (HR = 1.48, 95% CI 1.10-1.99), and age (HR 1.02/year, 95% CI 1.00-1.03) were independently associated with recurrence. A total of 668 (35.7%) patients died during follow-up. Recurrence significantly increased the all-cause mortality (HR = 2.55, 95% CI 2.04-3.18).

The risk of recurrent ischemic stroke or TIA was modest in our population and was associated with previously established risk factors. Recurrence more than doubled the all-cause mortality.

Paper III: Incidence and etiologies of stroke mimics after incident stroke or TIA

We identified 1872 patients who were discharged alive from our stroke unit after their index ischemic stroke or TIA during the inclusion period. During 8172 person-years of follow-up, 339 patients had 480 stroke mimic events. The cumulative incidence rate of stroke mimics during follow-up was 58.7 per 1.000 person-years (95% CI 53.7-64.2), compared with 34.0 per 1.000 person-years (95% CI 30.2-38.2) for recurrent stroke in the same time-period. As for recurrent stroke, the risk of stroke mimics was highest the first year after index ischemic stroke or TIA. The most frequent diagnoses were sequelae of cerebral infarction (19.8%), medical observation and evaluation for suspected cerebrovascular disease (15.6%) and infections (14.0%). The two most frequent and non-specific diagnoses (sequelae of cerebral infarction and medical observation etc.) were clustered in the first months after index stroke.

Stroke mimics after initial ischemic stroke are more frequent than recurrent stroke and the risk is especially high in the early period after stroke. Stroke mimics are multi-etiological in nature and non-specific diagnoses are most frequent directly after index stroke.

Discussion

Early recurrent ischemic stroke or TIA

The incidence rate of 30-day recurrence of ischemic stroke or TIA in our hospital-based cohort was 1.8%. There is scant information on early or late stroke recurrence in Norway, but our rate is among the lowest recurrence rates compared to previous studies that reported incidence rates between 1.6-15%.[15, 76, 159-161, 174, 179, 184, 185, 189-191, 193, 194, 200, 234-236] Comparability of results is limited in these studies due to differences in methodology, follow-up and populations. Table 1 demonstrates the 30-day incidence across different studies.

Table 1. Overview of 30-day incidences of recurrent stroke across studies

Author, year	30-day incidence, %	Study	Type of follow-up
Sacco, 1989*	3.3	Stroke Data Bank	Follow-up at 3 months
Sacco, 1994*	6.0	NOMAS	Follow-up at 6 months/telephone
Lauria, 1995	1.9	Community-based	Readmissions/Referral via GP
Lin, 1996*	4.7	Framingham	Follow-up at 3 months
Rundek, 1998*	2.9	NOMAS	Follow-up
Petty, 1998*	4.4	Population study	Medical records review
Moroney, 1998*	4.4	Single stroke unit	Follow-up/interview at 90 days
Hardie, 2004	2.0	PCSS	Follow-up/interview
Modrego, 2004	2.1	Single stroke unit	Readmissions
Lovett, 2004*	4.2	OXVASC	Follow-up at 1 month
Coull, 2004	15.0	OXVASC	Referral via GP
Smith, 2005	4.2	Administrative	Readmissions, administrative data
Dhamoon, 2006*	1.5	NOMAS	Follow-up at 6 months
Bravata, 2007*	1.6	Administrative	Readmissions, administrative data
Xu, 2007*	5.5	Stroke Registry data	Follow-up at 2-3 months
Mohan, 2009	1.1	Stroke Registry data	Follow-up at 3 months
Burke, 2014*	5.0	Administrative	Readmissions, administrative data
Amarenco, 2016*	2.8	TIAregistry.org	Follow-up at 1 month

** Denotes studies on ischemic stroke only. Abbreviations: NOMAS, Northern Manhattan Stroke Study; PCSS, Perth Community Stroke Study; OXVASC, Oxford Vascular Study and the Oxfordshire Community Stroke Project;*

Most of these studies report a 30-day recurrence rates in the 1.5-5% range. Eight of the listed studies in the table are included in the previously mentioned meta-analysis by Mohan et. al. from 2011 that reported a pooled 30-day recurrence incidence rate of 3.1%.[168] Only two of the studies listed in the table was published in this decade. Lack of recent studies makes the impact of contemporary changes in risk factors and secondary prevention strategies on 30-day recurrence difficult to assess.

The wide variations in incidence between studies may be explained by differences in methodology and definitions of recurrent stroke. Most studies listed in the table were prospective with regular follow-up appointments where the possibility of recurrence was considered. The most widespread definition of recurrence were all of, or a combination of the following characteristics: neurologic deficit of vascular origin lasting at least 24 hours; located in a different vascular territory; or being of a different subtype.[15, 161, 184, 185, 194, 200, 234] Some studies excluded events during the first 21 days.[160, 184] Some studies only included minor stroke or TIA.[174, 189] The use of CT and or MRI were also variable across studies. The most recent study, by Amarenco et. al, defined recurrence also as a symptomatic deterioration of previous neurologic deficits accompanied by neuroimaging evidence of new brain infarction. This is a sensible approach, considering that a cerebral infarction is a dynamic process that may evolve during the first days/weeks. A study that investigated new ischemic lesions in patients with minor stroke or TIA with a follow-up MRI done 30 days after initial ischemic stroke or TIA, found that the majority of symptomatic events were rated as progression of the original infarct and that events outside of the initial vascular territory were rare.[237]

Of the listed studies, 6/18 included also patients with hemorrhagic stroke at index. Hemorrhagic stroke constitutes 10-15% of all stroke, which implies that most patients in these studies had ischemic etiology. The meta-analysis by Mohan et al. included studies with all stroke types and found no differences in recurrence rates at 1 year between studies reporting recurrence after ischemic stroke only, compared with studies also including hemorrhages. Differences in incidence of recurrence rates between ischemic stroke and ICH were not assessed at earlier time-points like 30 days. If the early recurrence rate of hemorrhagic stroke differs significantly from ischemic, it may have influenced the reported 30-day recurrence rate in these studies. In addition, since hemorrhagic stroke has higher early mortality than ischemic stroke, a selection bias may also be present. Unfortunately, even less is known about early recurrence of hemorrhagic stroke than ischemic. A meta-analysis reported an annual

risk of recurrence after spontaneous ICH between 1.3-7.4%, but most of these studies started follow-up at 30 or 90 days after the hemorrhage.[238] One recent study investigating recurrence up to 5 years after primary ICH reported the cumulative recurrence risk of ICH after 28 days being 3.67% (95% CI 3.37-3.97),[239] which is comparable to many ischemic stroke studies.

Two studies reported 30-day recurrence after minor stroke or TIA (mRS 0/1 or NIHSS <4). About half of our study population had these characteristics. These two studied reported discrepant 30-day recurrence rates. The study by Coull et al. reported the highest rate by far with a 15% risk of 30-day recurrence.[189] This study from the early 2000s on 174 patients (87 minor stroke and 87 TIAs) included patients in an era where guidelines recommending that TIA patients should be assessed within two weeks. In fact, several patients suffered recurrence before they were even seen by a physician. The most recent study on 4789 patients, by Amarenco et al., where patients were assessed within hours or next day, reported a recurrence rate of 2.8%, which is more in line with other results.[189]

Factors associated with early recurrent stroke

In our study, patients with large-artery atherosclerosis had the highest risk of 30-day recurrence. This is in line with results from other studies reporting 30-day recurrence stratified by stroke subtype. Sacco et al. reported that patients with atherosclerosis had a 30-day recurrence risk of 8% in one study, and 14% in another.[194, 234] Lacunar stroke had the lowest risk of early recurrence in these studies. Moroney et al. reported that atherothrombotic stroke mechanism had a RR of 3.3 (95% CI 1.3-8.3), which was higher than for atrial fibrillation.[200] Modrego et. al reported the highest 30-day risk of recurrence for cardioembolic stroke at 3.5%, higher than for atherothrombotic at 2%.[185] In the most recent study, Amarenco et al. found that large-artery atherosclerosis is a stroke subtype that is associated with a significantly higher risk of recurrence compared with other etiologic stroke subtypes.[174] In a study including only patients with LAA, with symptomatic carotid stenosis, Strömberg et al reported a 30-

day recurrence of 7.5%, higher than most estimates on general stroke populations.[240] Rapid carotid endarterectomy (CEA) is highly effective for reducing recurrent stroke in selected patients with stenosis of the internal carotid artery.[241] The possible consequences may be demonstrated in paper I, as four of five patients found eligible for CEA, suffered a recurrent stroke within 30 days before surgery.

In paper I, we demonstrated that a significant part of patients with recurrence had intracranial artery stenosis (ICAS). ICAS has a high risk of recurrent stroke in the same vascular territory.[242] Ovesen et al. reported a higher risk of recurrence in stroke patients if intracranial atherosclerosis were detected during acute evaluation for stroke.[243] In a sub-analysis of the "Prospective study of symptomatic atherothrombotic intracranial stenosis" (GESICA), Mazighi et al. reported a 2-year risk of recurrent stroke in the territory of an symptomatic intracranial stenotic artery to be 38% despite medical therapy, which is much higher than for ischemic stroke in general.[244] Still, the risk of early recurrence in patients with ICAS is poorly studied. In a sub-study of the "The Warfarin-Aspirin Symptomatic Intracranial Disease" (WASID) study, Ovbiagele et al. found a 30-day risk of ischemic stroke in the arterial territory of the symptomatic stenotic intracranial artery to be between 3-9.5%, depending on the type of index event (TIA, ischemic stroke or both).[245] In a study on patients with clinical TIA attributable to intracranial artery disease, but with lesions on DWI, the 90-day recurrence risk was 14.6%, with most patients experiencing recurrence during the first week.[246] Recognition of ICAS as the cause of ischemic stroke or TIA is important, as proper rapid medical treatment and risk factor control (e.g. blood pressure reduction) may reduce the risk of early recurrence.[247, 248]

Among factors associated with early recurrence, peripheral artery disease (PAD) was a predictor of early recurrence in the multivariate analysis in paper I. PAD is a common type of atherosclerosis that affects peripheral arteries. Presence of PAD, or low ankle-brachial index which is a measure of arterial stenosis in the lower extremities, is associated with increased risk of recurrent stroke.[249] A meta-analysis by Hong et al. demonstrated that the pooled hazard ratio for recurrent stroke in

patients with PAD was 1.70 (95% CI 1.1-2.6) compared with patients without PAD. One study by Tsivgoulis et al. that investigated the association between PAD and early ischemic stroke recurrence, demonstrated that patients with low ankle-brachial index had much higher cumulative 30-day recurrence rate (19.2%; 95%CI: 4.1–34.3) compared to the rest (3.3%; 95%CI: 0.4–6.2%; p = 0.001).[250] In total, atherosclerosis either as large-artery disease or intracranial disease, was found to be responsible for 21/33 (64%) of recurrent strokes in paper I. PAD is another manifestation of atherosclerosis and was present in 21% of patients with 30-day recurrence. It is therefore not surprising that there was an association between PAD and recurrence in the multivariate analysis.

In the multivariate analysis in paper I, stroke of other etiology was significant predictor of 30-day recurrence. This was due to a significant number of patients (6/33, 18%) with recurrence having cancer as the suspected underlying cause of both the index and recurrent strokes. With an aging population, cancer incidence is rising resulting in an increasing proportion of patients susceptible to cancer associated stroke. On autopsy, 15 % of cancer patients have evidence of cerebrovascular disease.[251] Twenty percent of all deep vein thrombosis (DVT) and pulmonary embolisms are diagnosed in cancer patients.[252] Although there is no consensus on diagnosis of cancer-related hypercoagulability, these patients often have migratory thrombosis, high D-dimer levels, and multiple arterial or venous events in several vascular territories.[252, 253] Cancer of lung, pancreas and gastrointestinal tract are the most common causes of cancer-related hypercoagulability.[252] In paper I, of the six cases recurring the first 30 days due to cancer-related stroke, three patients had pulmonary cancer, two pancreatic, and one thyroid. Only one patient was recognized as having cancer-related stroke and classified as SOE at index event. Three were classified as CE and two as SUE. In 5 of 6 patients, a primary tumor was identified by CT, in the last one, a thyroid tumor was diagnosed with a PET scan. Of six patients diagnosed with cancer related stroke and recurrence, five had multiple infarctions and clinical symptoms from several vascular territories, three patients presented with DVT and/or PE during index or second admission and all had elevated D-dimer levels on index stroke admission, half of which above the upper detection

threshold of 20 mg/L. In clinical practice, patients with cancer associated stroke are known to be prone to recurrence, but only a few reports about recurring stroke in cancer patients exist. In a study from 1994, 2 of 33 cancer patients suffered recurrent stroke during an average follow-up of >9 months.[254] In a more recent study, the authors reported 36 recurrent ischemic strokes in 263 patients with a median survival of 84 days.[255] With proper etiological investigation and focus on other signs and symptoms of hypercoagulability (e.g. migratory thrombosis, high D-dimer levels), stroke recurrence might be prevented by early diagnosis of cancer and administration of anticoagulation.

In paper I, after re-evaluation, we found a common subtype for index and recurrent stroke in all but one patient. Recurrent stroke seem to be predominantly of the same subtype as the first or index stroke, although few studies have explored this matter.[187, 199, 201, 256] Especially cardioembolic stroke demonstrate a tendency to recur as the same type, reported in 77-94% of cases in some studies.[187, 199, 201] Small-vessel occlusion or lacunar infarction seem to have the lowest risk to recur as the same subtype.[187, 199, 201, 256] No studies seems to have explored the correlation of subtypes of early recurrence. Assuming that recurrent ischemic stroke or TIA within 30 days would be caused by the same pathological process in most cases, we investigated if the TOAST classification system could accurately determine the etiological subtype already at index stroke.

Table 2 demonstrates the differences in etiologies classified by TOAST between the index and the recurrent event.

Table 2. Differences in TOAST etiology classification between index and recurrent event.

Etiology (TOAST)	Index, n (%)	Recurrence, n (%)
Atherosclerosis (LAA)	13 (39.4)	21 (63.6)
Cardioembolism (CE)	5 (15.2)	4 (12.1)
Small vessel disease (SVO)	1 (3.0)	1 (3.0)
Other determined (SOE)	2 (6.0)	6 (18.2)
Undetermined (SUE)	12 (36.4)	1 (3.0)

In our data, by classifying etiology with TOAST, stroke due to LAA was underclassified as cause at index and many patients with LAA were classified in the SUE group, despite demonstrating pathology of extra- or intracranial arteries. Adams et al. formulated the following in their original publication on TOAST; *"The diagnosis of stroke secondary to large-artery atherosclerosis cannot be made if duplex or arteriographic studies are normal or show only minimal changes."*[48] By using nothing but the grade of stenosis (> 50%) as the foundation of LAA-classification, newer insights into the pathophysiology of atherosclerosis and plaques are overlooked. Improvements in imaging techniques such as high-resolution MRI angiography, contrast-enhanced ultrasonography and PET/CT have evolved the concept of plaque vulnerability.[73] Presence of plaque characteristics such as ulceration, intraplaque hemorrhage, slim cap thickness and a lipid-rich necrotic core are associated with an increased risk of plaque rupture even in non-stenotic arteries.[72, 73, 257]

TOAST is primarily a research tool. In clinical practice, the stroke neurologist should properly evaluate even minor atherosclerotic intra- or extracranial pathology in order to determine the correct secondary prevention treatment in each case. Still, our results demonstrate that stroke patients without "significantly" stenotic atherosclerotic disease or malignancies are at high risk of early recurrence. Classifying such cases in the SUE category may undercommunicate the severity of their pathological process.

Long-term recurrent ischemic stroke or TIA

In paper II, we reported the long-term recurrence rates of recurrent stroke. The cumulative incidence of first recurrence by years after index stroke in our stroke unit are demonstrated in table 3.

Table 3. Cumulative incidences of first recurrent ischemic stroke or TIA by years after index stroke from the NOR-STROKE registry

Years after index	Rate, (%)
1	5.4
2	7.3
3	8.7
4	10.3
5	11.3
6	12.3
7	13.0
8	14.2
9	14.2

The cumulative incidence of first recurrent ischemic stroke or TIA was highest the first year after index ischemic stroke or TIA, and the rate of recurrence stabilized after about 4 years. At the end of follow-up, the risk of having at least one recurrent ischemic stroke or TIA was 14.2%.

Table 4 demonstrates 5-year recurrence rates reported in other studies.[15, 160, 172, 173, 176, 188, 194, 198, 201, 207, 258-264]

Table 4: Overview of 5-year incidences of recurrent stroke across studies

Author, year	5-year recurrence, %	Study	Type of follow-up
Sacco, 1982	42/24	Framingham	Regular follow-up
Meissner, 1988	19.3	Rochester	Regular follow-up
Viitanen, 1988	37	Population-based	Regular follow-up?
Burn, 1994	30	OXVASC	Regular follow-up
Sacco, 1994*	25	NOMAS	Regular follow-up
Hankey, 1998	22.5	PCSS	Regular follow-up
Petty, 1998*	39.3	Rochester	Regular follow-up
Eriksson, 2001	38.7	Single stroke-unit	Regular follow-up
Modrego, 2004	26.0	Single stroke-unit	Readmissions
Hata, 2005	51.3	Population-based	Regular follow-up
Dhamoon, 2006*	18.3	NOMAS	Regular follow-up
Mohan, 2009	16.2	Stroke Registry data	Regular follow-up
Lewsey, 2010	10.8	Country-wide	Readmissions, administrative data
Sun, 2013	18.4	Multi stroke-units	Readmissions, administrative codes
Pennlert, 2014	18	WHO MONICA	Regular follow-up
Li, 2015*	20	OXVASC	Regular follow-up
Edwards, 2017	7.8	Single stroke-unit	Readmissions, administrative data
Amarenco, 2018*	9.5	TIAregistry.org	Regular follow-up
Salehi, 2018	14.5	Stroke Registry data	Regular follow-up?
Zhao, 2019	26.3	Population based	Regular follow-up

** Denotes studies on ischemic stroke only. Abbreviations: OXVASC, Oxford Vascular Study and the Oxfordshire Community Stroke Project; NOMAS, Northern Manhattan Stroke Study; PCSS, Perth Community Stroke Study; WHO MONICA (Multinational Monitoring of Determinants and Trends in Cardiovascular Disease) Project;*

Compared with studies on early recurrence where only 6/18 of the examined studies included patients with hemorrhagic stroke at index and/or recurrence, 15/21 studies reporting 5-year recurrence rates included hemorrhagic stroke at index and/or follow-up. Five of the studies mentioned in the table were included in the meta-analysis by Mohan et al. that reported a cumulative 5-year recurrence risk of 26.4%.[168]

As for early recurrence, differences in study populations, follow-up, definitions of recurrence and inclusion of hemorrhagic stroke may explain some of the observed differences between studies.

The more recent studies demonstrated in table 4 show in general lower incidences of recurrence, except studies from Asian populations. Still, studies on stroke recurrence trends differ on whether recurrence rates are declining in industrialized countries.[168, 265, 266] Some studies from selected populations indicate a decline in recurrence rates,[175, 267-269] other have reported an increase in incidence,[263, 270] but a recent meta-analysis estimated the annual recurrent stroke risk to be ≈4.26% without any observable decline over time.[266] A study from the Dijon Stroke Registry reported an increase in recurrent strokes due to improved stroke care and more stroke survivors with longer survival, which is relevant with populations ageing in industrialized countries.[270] On the other hand, a Swedish study found a reduction in incidence of both first and recurrent stroke, concluding that there were no indications of an increased stroke burden.[269] More studies are needed on this matter.

Factors associated with long-term recurrent stroke

In paper II, we investigated the factors associated with recurrent ischemic stroke or TIA in our population and found that age, prior stroke, hypertension and chronic infarcts on MRI were predictors of recurrence. Hypertension at index event was the strongest risk factor for long term recurrence in paper II, with a HR of 1.65 (95% CI 1.21-2.25). In one of the first longitudinal studies on stroke recurrence from Framingham, Sacco et al. found that the presence of hypertension at index was strongly associated with the risk of recurrence, especially in men.[188] In a publication based on the Northern Manhattan Stroke Study, Sacco et al found that hypertension was a predictor of overall recurrence with a HR of 1.6 (95% CI 1.01-2.6).[194] Mohan et al. found that hypertension increased the risk of recurrence at 5 years with a HR of

1.47 (95% CI 1.1-2.0).[160] Erikson and Olsson found systolic blood pressure as a predictor of recurrent stroke, with an OR of 1.005 (95% CI 1.003-1.007) per mm Hg increase.[260] In several studies that reported hypertension as a predictor of long-term recurrence, the impact of hypertension was quite similar to our findings.

Since patients with ischemic stroke or TIA are as previously mentioned at high risk of suffering another stroke compared to the general population, it is not unexpected that prior ischemic stroke or TIA and chronic infarcts on MRI was a predictor of long-term recurrence in paper II. Most studies on long-term recurrence in table 4 included only patients with "first stroke", which implies that these patients did not have ischemic stroke or TIA prior to inclusion.[15, 160, 168, 172, 173, 178, 201, 207, 258, 261]. Still, some studies have assessed the impact of prior stroke on long-term recurrence. In the study by Eriksson et al., 23.3% of patients had a history of stroke and prior stroke was a predictor of recurrence with a OR of 1.52 (95% CI 1.03-2.23).[260] In the study by Edwards et al. prior stroke had a HR of 5.1 (95% CI 4.8-5.5) for a new stroke 5 years post-stroke compared to stroke-free matched controls.[264] No other studies on long-term recurrence included chronic infarcts on MRI in their analysis. Several studies have examined the concept of silent brain infarction (SBI). Leary et al. estimated that SBI is far more common than symptomatic lesions, with approximately 11 million first ever SBI´s in the US in 1998, compared with 770.000 symptomatic infarctions.[271] In our study population, we were not able to discriminate between symptomatic and silent lesions. Thus, according to our findings, the presence of a chronic infarct on MRI in a patient with incident stroke or TIA, is suggesting a heightened risk of recurrent stroke.

Although we did not find male sex as a predictor of having recurrent ischemic stroke or TIA at the $p<0.05$ level, several other publications have reported this association. As mentioned previously, males have a higher stroke incidence than females,[94] but whether this also applies to recurrent stroke or not is unclear. In the early publication from the Framingham study, the risk of recurrence adjusted for age was significantly higher in males than females (42% vs 24%).[188] Meissner et al. reported 5-year recurrence rates of 21% for men and 17% for women.[258] A study by Moroney et al.

reported on the contrary that female sex was a predictor of recurrent stroke during a follow-up period of up to 59 months.[272] Several other studies have reported similar recurrence rates between males and females.[15, 178, 260]

In contrast to 30-day recurrence (Paper I), stroke subtype was not a predictor of long-term recurrence in our study. This is in line with most other studies on long-term recurrence,[15, 160, 173, 194, 198, 207, 262] although Hata et al. reported that CE had a higher 10-year recurrence rate than lacunar infarction (HR 1.76, 95% CI 1.00-3.11). Some studies have claimed that lacunar stroke carried a better prognosis than other subtypes, but this in not supported by the currently available studies on long-term recurrence.[204]

Several other studies have found cardiac disease a risk factor for long-term recurrent stroke. Sacco et al. found in the Framingham study that cardiac comorbidity was associated with an increased risk of recurrence.[188] Viitanen et al. found cardiac failure to be associated with recurrent stroke.[259] Modrego et al. found patients with combination of AF and other cardiac disease to have increased risk of recurrence with cardioembolic stroke.[185] Mohan et al. found AF as a risk factor of 5-year recurrence.[160] In general, cardiac disease may be seen as a result of underlying atherosclerotic, hypertensive and inflammatory processes which also play a major part in the formation of cerebrovascular disease. Thus, an association between cardiac disease and stroke recurrence is likely.

Several other factors such as smoking, alcohol overuse, diabetes and stroke severity have been inconsistently associated with long-term recurrence in studies in table 4, but was not significant predictors in our patients.

Table 5 demonstrates the incidence of all 277 recurrent ischemic stroke or TIA from paper II by year after index stroke per 1000 years of follow-up, estimated with the Andersen-Gill model.

Table 5, incidence rates of all recurrent ischemic stroke or TIA by year after index.

Year after index	Person-time (years)	Recurrences (n)	Rate	95% Conf. Interval
0 - 1	1741.8	118	67.7	56.6 - 81.1
1 - 2	1608.1	51	31.7	24.1 - 41.7
2 - 3	1476.2	31	21.0	14.8 - 29.9
3 - 4	1192.6	30	25.2	17.6 - 36.0
4 - 5	867.8	20	23.0	14.9 - 35.7
5 - 6	605.9	13	21.6	12.4 - 37.0
6 - 7	395.7	8	20.2	10.1 - 40.4
7 - 8	219.1	5	22.8	9.5 - 54.8
8 - 9	65.2	1	15.3	2.2 - 108.9
> 9	0.5	0	0.00	. - .
Total	**8172.9**	**277**	**33.9**	**30.1 - 38.1**

By this method, the recurrence rate is especially high the first year of follow-up, with more similar rates the following years.

Mortality

In paper II, 36% of the cohort died during follow up, resulting in cumulative all-cause mortality of 10.7% at 1 year 33.5% at five years after index ischemic stroke or TIA. As the risk for recurrence, the risk of death was the highest early after index. This is also reported in other studies that have reported an elevated mortality risk especially the first year after stroke, ranging up to 10 times higher compared to the general population in some studies[32, 42, 273-276]. In 1-year survivors, the subsequent mortality risk seems lower, but all-cause mortality after ischemic stroke is considerably elevated years after the event in comparison with the general population. Hardie et al. reported an annual death rate of 4.8% among 1-year survivors of stroke, 2.3 times

greater than for the general population.[33] In a study that compared long-term mortality after ischemic stroke with age-matched controls, Carter et al. reported a more that 3-fold risk of death in ischemic stroke patients.[277] In a Norwegian study, Mathisen et al. found a HR of 2.2 for death long-term after ischemic stroke, compared with stroke-free individuals.[43] Other studies have also reported a 2-3 times higher long-term mortality after stroke compared with the general population.[31, 273, 274]

Table 6 demonstrates reported 5-year mortality rates across studies on long-term mortality after stroke. Most studies are based on cohorts followed in the 1980s and 1990s, with just a few recent studies. Although there are differences in populations and inclusion of ICH, the reported mortality rates are strikingly similar. Only 5/17 included only patients with ischemic stroke or TIA as the primary event.

Table 6, 5-year mortality rates reported across studies

Author, year	5-year mortality, %	Study
Sacco, 1982	48/40	Framingham
Schmidt, 1988	72.1	Stroke Registry
Kojima, 1990	60.8	Community-based
Dennis, 1993	45	OXVASC
Sacco, 1994*	45	NOMAS
Petty, 1998*	52.9	Rochester
Hankey, 2000	60.1	PCSS
Brønnum-Hansen, 2001	60.0	WHO MONICA
Hartmann, 2001*	41	NOMAS
Kiyohara, 2003	59.7/67.7	Community-based
Hardie, 2003	59	PCSS
Bravata, 2003*	52.6	Administrative
Vernino, 2003*	54	Population-based
Kammersgaard, 2006	54.8	Copenhagen Stroke Study
Wolfe, 2011	57.2	Stroke Registry data
Ray, 2013	59.4	Community-based
Mathisen, 2016	26.7	Stroke unit

** Denotes studies on ischemic stroke only. Abbreviations: OXVASC, Oxford Vascular Study and the Oxfordshire Community Stroke Project; NOMAS, Northern Manhattan Stroke Study; PCSS, Perth Community Stroke Study; FUTURE, (Follow-Up of Transient Ischemic Attack and Stroke Patients and Unelucidated Risk Factor Evaluation) study; WHO MONICA (Multinational Monitoring of Determinants and Trends in Cardiovascular Disease) Project;*

Mortality after stroke is mainly due to cardiovascular causes and is consistently associated with cardiovascular risk factors across studies.[15, 33, 39, 42, 45, 188, 194, 273, 274, 276, 278-282] One of these cardiovascular causes is recurrent stroke, but despite recurrence being frequent and devastating, few studies have assessed the impact recurrent stroke has on all-cause mortality. In one of the first studies investigating this matter, Sacco et al. found no difference in mortality for incident ischemic stroke compared with those with prior stroke in the NOMAS study.[194] Jorgensen et al. found in the

Copenhagen Stroke Study that mortality was almost doubled in patients with recurrence compared with patients with a first-ever stroke (OR 1.8 (95% CI 1.26-2.66)).[217] Several other studies have also reported increased mortality after recurrence. Petty et al. found that recurrence tripled the risk of death after first cerebral infarction in a population from Rochester, Minnesota (RR 3.0 (95% CI 2.5-3.5)).[15] Lisabeth et al. reported that recurrence increased the risk of mortality with a risk ratio of 2.67 (95% CI 1.90-3.76) in a Hispanic and white population.[218] In a recent Finnish study on young stroke patients, Aarnio et al. found that recurrent stroke was the most important risk factor for mortality after first-ever ischemic stroke (HR 16.68 (95% CI 2.33–119.56).[219] These studies differ in populations, time periods and importantly – statistical methods. Since the risk of recurrence varies by time after the index event, it violates the proportional hazards assumption in the Cox regression model. If this problem is not taken into account in the model, then the regression result will not be valid for this factor. This is usually solved by including this factor as a time-varying covariate in the Cox model. Two of the mentioned studies, by Lisabeth et al. and Petty et al., addressed this issue and adjusted their regression analyses accordingly. Their results are similar and in line with our findings.

Recurrence seems to impact mortality by increasing disability. Stroke severity, manifested as the neurological deficits or degree of disability, is considered the most important factor affecting mortality in stroke patients.[44, 278, 283] When ischemic stroke adds on to existing disability from any cause, it increases mortality, both short- and long-term. Kwok et al. found in a study from the UK that prestroke disability predicted inpatient mortality independent of stroke type and severity.[284] Hankey et al. found in the Perth Community Study that a reduced Barthel Index (<20), doubled the long-term mortality risk.[273] In a recent publication from OXVASC, Ganesh et al. found increasing 5-year mortality for every point increase in pre-stroke modified Rankin Scale.[285] Unfortunately, most trials on thrombolysis in acute stroke excluded patients with a modified Rankin Scale ≥2.[285] This has been implemented in the European guidelines as a recommendation that primarily patients with a premorbid

modified Rankin Scale 0-1 should be eligible for acute interventions.[286] The implication of this practice is that patients with a substantial prestroke morbidity is adding even more disability which a subsequent increase in mortality.

Secondary prevention of ischemic stroke or TIA

In paper II, we demonstrated that the patients in our study had high rates of prescribed secondary prevention therapies such as antiplatelet or anticoagulant treatment, lipid-lowering drugs and antihypertensive drugs. Ideally, all patients should receive the optimal combination of secondary prevention and adhere to it for maximal risk reduction. This is not always the case due to differences in factors like guideline adherence, drug adherence and tolerance, or incomplete stroke evaluation. As previously mentioned, there is evidence that optimal secondary prevention is associated with a lowered risk of stroke, major vascular events or death.[26, 167, 287] Still, little is known about the rates and trends of secondary preventions therapies after ischemic stroke across countries and populations. In a publication from the PURE study, Yusuf et al. found higher rates of secondary prevention therapies in high-income countries (e.g. Sweden) compared to low-income countries.[288] Data from the OECD Health Statistics database demonstrate significant differences in drug consumption between the European countries.[289] According to this report, consumption of antihypertensives was below average for the Norwegian population as a whole in 2015-16, while consumption of lipid-lowering drugs was significantly above average.[290] In patients with ischemic stroke or TIA in Norway, national data on dispensing of secondary prevention drugs in cardiovascular disease has been only recently available. Figure 3 demonstrates the percentage of patients with recent ischemic stroke or TIA that filled their prescription of different drug classes within 90 days after hospital discharge in 2012-13.[291] Nationwide, over 90% with ischemic stroke filled their prescription of antithrombotics (B01) within 90 days. The rates in TIA patients were slightly lower. Compared to the national data, patients in paper II

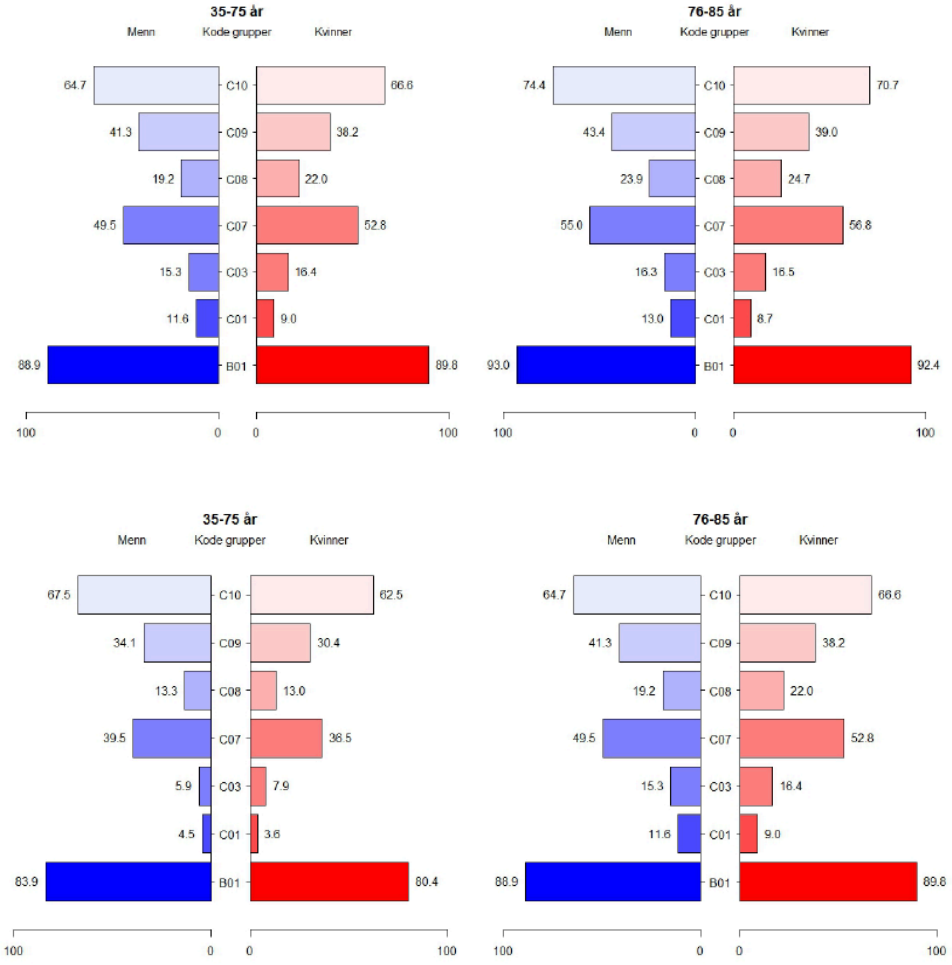
had higher prescription rates for antithrombotics, but similar prescription rates for both lipid-lowering drugs (C10) and antihypertensive drugs (C08-09).

Despite the fact that most patients are prescribed secondary prevention, we do not know if the patients actually were taking all or some of their prescribed drugs. In the stroke unit at Haukeland University Hospital, most patients are followed up after 3 months by a stroke neurologist in an out-patient setting where drug compliance or changes in prescriptions are noted. In this setting, most patients seem to adhere to their medications. Otherwise, patients are followed up in general practice, where the intensity of follow-up is both physician- and patient-dependent. On the other hand, our recurrence rates are in the anticipated range with regards to the expected effects of secondary prevention therapies. Older studies on the natural history of ischemic stroke before secondary prevention, showed 5-year recurrence rates of around 40%. This may suggest that patients in our cohort comply with their secondary prevention therapies.

Studies demonstrate that many patients do not adhere to secondary prevention therapies. In a meta-analysis of non-adherence to secondary prevention after stroke or TIA, Al AlShaikh et al. found that the non-adherence rate was 30.9% across 16 included studies.[292] A meta-analysis by Chowdhury et al. found that suboptimal adherence to cardiovascular mediations in patients with cardiovascular diseases, including stroke, is responsible for around 9% of all cardiovascular events in Europe.[293] Sappok et al. reported that compliance with secondary prevention after stroke in an urban German population was better especially in patients with higher age, more severe neurological deficits and cardioembolic stroke.[294]

Even when patients comply with their secondary prevention therapies, many patients do not reach the recommended target values for blood pressure or lipids. In a recent Norwegian study from a General Practice, 47% of patients reached their target blood-pressure and 27% their target low density lipoprotein (LDL) cholesterol target value during first year of follow-up.[295]

Figure 2: Norwegian national dispensing data for secondary prevention drug classes (WHO Anatomical Therapeutic Chemical Classification (ATC) B01-C10) in ischemic stroke (top) and TIA (bottom) survivors, stratified by age group and sex. Percentage (%) of patients that filled their prescriptions within 90 days after ischemic stroke or TIA discharge in 2012-2013.[291]



Left: Patients 35-75 years of age. Right: patients between 76-85 years of age. Blue: men. Red: women. ATC drug classes: C10, Statins and other lipid-lowering drugs; C09, ACE inhibitors/Angiotensin II-receptor blockers including combinations with diuretics; C08, Calcium antagonists; C07, Beta blockers; C03, Diuretics; C01, Cardiac medications; B01, Antithrombotics.

Stroke mimics

In paper III we estimated the incidence of stroke mimics after ischemic stroke or TIA. Our study is the first to calculate the cumulative risk of stroke mimic in a stroke population. Stroke mimic patients represent up to 40% of all patients admitted with suspected stroke.[222] Many studies have observed that patients with stroke mimics have fewer ischemic stroke risk factors.[220, 226, 296, 297] Prior studies have quantified the incidence of stoke mimics by reporting the proportions of stroke mimics in all suspected strokes in admitted to emergency departments or stroke units. About one of 12 patients had been admitted with a stroke mimic within the first year and one of six patients had been admitted within five years after the index stroke.[224, 298]

In our study, patients with stroke mimics had more often hypertension at the time of the index stroke. Patients with hypertension are susceptible to both severely elevated blood pressure that can cause neurological symptoms, as well as hypotension due to intake of vasoactive drugs, which may lead to unexpected drops in blood pressure with altered consciousness, dizziness and syncope. Diabetes was also more common in patients with stroke mimics. Hypo-/hyperglycemia can produce a wide array of focal and global neurological signs. We did not, however, register blood pressure levels or serum glucose levels for each admission and could not examine these factors.

We found a multitude of stroke mimic diagnoses after ischemic stroke. In paper III, due to article length restrictions, only the seven most common diagnoses were listed. Table 7 demonstrates all the different stroke mimic diagnoses in paper III, except the diagnoses with only one occurrence, which were grouped together.

Table 7: Frequency of stroke mimic diagnoses and the corresponding ICD-10 codes at discharge

Diagnoses	**N**	**ICD-10**
Sequelae of cerebral infarction	95	I69.3
Medical observation and evaluation for suspected cerebrovascular disease	75	Z03.3
Infections	67	N39, J18, J06, A41,
Epilepsy and recurrent seizures	46	G40, R56
Dizziness and vertigo	40	H81, H83, R42
Migraine and other headaches	37	G43, R51
Syncope and collapse	34	I95, R55,
Other diagnoses (n=1 each)	17	miscellaneous
Disorientation and confusion	13	G45, R41, F03
Heart disease (CHD, heart failure, arrhythmias)	12	I21, I50, I45
Falls and injuries	10	S06, S52, S72, W19,
Hemorrhagic complications (GI, extra-axial ICH, other)	9	H11, I62, K92
Drug side-effects	8	Y4n
Cancer	5	C00-C97
Diabetes	4	E10-E14
Venous thromboembolic disease (pulmonary, cerebral sinus)	3	I26, G08
Depression/anxiety	3	F30-F48
Anemia	2	D50-D53

Abbreviations: N, Number; ICD-10, International Classification of Diseases, Tenth Revision; CHD, coronary heart disease; GI, gastrointestinal; ICH, intracerebral hemorrhage;

Admissions with suspected stroke after ischemic stroke or TIA were common in our study population and the risk is also highest shortly after index stroke discharge.[299] Fear of recurrent stroke is also common among stroke patients. In a small study by Townend et al. 50 out of 89 stroke survivors were worried about suffering another stroke.[300] Although there seem to be no data on this subject, one implication of fear of

recurrent stroke may be that stroke survivors are more prone to seek acute medical help for new or re-expressed symptoms. One could also hypothesize that the fear would naturally be most intense shortly after the stroke. This may thus provide an explanation on why the two most common and unspecific diagnoses were especially frequent in the first months and year after the index event.

The most common specific stroke mimic in our study was infection. An infection may cause stroke-like symptoms if it affects a patient's consciousness directly, such as meningitis or encephalitis, or by the phenomenon of re-expression of prior stroke symptoms, or post-stroke recrudescence.[228, 301, 302] Infections are frequent after stroke, partly because of immunodepression caused by central nervous system damage and also the direct effects of stroke, such as the risk of aspiration.[303, 304] Because blood tests and identification of infectious agents are time-consuming procedures, these patients may end up being treated with thrombolysis or hospitalized even with simple infections. Few studies have investigated long-term incidences of common infections after stroke. A Norwegian study on readmissions up to 10 years after stroke found that infections were the cause of 17.3% of post-stroke readmissions, peaking in incidence about 6 months after stroke with a subsequent stabilization in incidence.[303] We found the same pattern in frequency for infections as stroke mimics.

The second most common specific stroke mimic was seizures and epilepsy. Seizures are common stroke mimics and are challenging to distinguish from acute stroke as they may cause focal neurological symptoms, as well as altered consciousness.[221] Seizures/epilepsy peak in occurrence between 6 and 12 months after stroke,[305] and the same peak is observed for seizures as a stroke mimic in our study.

Both dizziness/vertigo and syncope/collapse are common stroke mimics, as they may produce neurological symptoms that are difficult to separate from acute stroke.[221, 223] In our study, these mimic diagnoses were spread out over the follow-up period without any clustering early after index stroke. One explanation for this might be that these symptoms are common in an ageing population. They are often caused by a

general decline of the vestibular system function, leading to vertigo, imbalance and falls, and not necessarily affected by the index stroke.[306]

We found migraine and other headaches, which often are suspected to be a symptom of extra- or intra-axial hemorrhages after stroke, to be a common stroke mimic in our population. Migraine with aura is considered a risk factor for stroke.[307, 308] Moreover, migraine is also the third most common stroke mimic and a frequent cause for erroneous thrombolysis.[309] Because both migraine and ischemic stroke are prevalent diseases, the difficulty of discerning a migraine attack from an ischemic event is commonplace in a stroke unit. Besides, while thrombolysis in migraine patients is considered safe,[309] this applies primarily to patients without prior stroke.

Most stroke mimics diagnoses in paper III were done without exclusion of diffusion restriction abnormalities on MRI. Although almost 90% of patients underwent brain imaging, most of them were examined only with CT, which have lower sensitivity for acute stroke detection, especially in the early phase. Accordingly, most stroke mimics diagnoses were made by a combination of clinical judgment and other diagnostic modalities, like blood tests, EEG etc. This implicates that we cannot exclude that some ischemic stroke or TIA events may have been missed, which would overestimate the incidence of stroke mimics and underestimate the incidence of recurrent ischemic stroke or TIA. On the other hand, most patients were treated in a stroke unit by an experienced stroke neurologist and the results in paper III is thus the expression of their clinical judgment and their real-world use of imaging studies. Many of the diagnoses in table 7 seem to be possible to diagnose without the need of excluding stroke on DWI-imaging.

In other studies, some authors have used the term ”neuroimaging-negative” ischemic stroke for patients that were thought to have ischemic stroke, but lacked diffusion restriction abnormalities on DWI-MRI after rapid treatment with tPA.[297, 310, 311] We cannot exclude that this may have occurred in some of the 38% of stroke mimic patients with a negative DWI-study, but according to a study by Freeman et al., this phenomenon is very rare.[312]

The process of ruling out ischemic stroke in a patient with acute focal neurological signs often requires observation combined with brain imaging, due to the non-specific nature of neurological symptoms. This indicates that hospitalization of stroke mimics is impossible to avoid entirely, but better education of patients, family and healthcare professionals may have the potential to avoid unnecessary admission after ischemic stroke, especially in the early phase.

Future perspectives

Over the last decades, there has been an improvement in acute ischemic stroke treatment, improved control of cardiovascular risk factors and an increase in life expectancy both in Norway, and in many other populations.[27, 99, 313, 314] This implies that ischemic stroke patients in the future will live longer, with less neurological sequelae and have a higher quality-of-life. These patients are projected to suffer both more recurrences and more hospital admissions with stroke mimics.[223] Knowledge about the risk, the risk factors and the consequences of recurrence and stroke mimics is of value for every clinician treating ischemic stroke patients.

In most stroke units, the standard evaluation for acute stroke at admission is CT with or without contrast angiography, which is excellent to exclude hemorrhages and other pathologies, but have lower sensitivity for detection of acute ischemic stroke. Some have advocated the use of CT perfusion and especially diffusion-weighted MRI to discriminate between acute ischemic stroke and stroke mimics,[315, 316] but there are still several issues with implementing more advanced imaging modalities in an acute stroke protocol, such as costs and availability. However, implementation of such diagnostic modalities in acute stroke evaluation could potentially reduce possibly harmful recanalization therapy of patients with stroke mimic shortly after ischemic brain injury.

Now that we see the evolution of personalized medicine, assessment of a patient's risk combined with their genetic profile will open new possibilities for individually tailored and even more effective secondary stroke prevention. Because in contrast to acute ischemic stroke therapies, few novel therapies have been adapted for secondary prevention the last decades. There are a few glimpses of hope though. Recently, studies on both novel therapies and combination of existing therapies have shown the potential to significantly reduce the risk of recurrent cardiovascular events compared with existing therapies. A study on reducing inflammation in patients with atherosclerotic disease with a monoclonal antibody demonstrated a major reduction in cardiovascular events after 48 months.[317] Monoclonal antibodies that inhibits proprotein convertase subtilisin–kexin type 9 (PCSK9) have the potential to lower LDL-cholesterol levels far below the current LDL-level treatment goals, thereby reducing the risk of recurrent cardiovascular events even more than with statin therapy.[318, 319] Another recent study showed a benefit of adding low-dose anticoagulant therapy (rivaroxaban) to aspirin for the reduction of cardiovascular outcomes in patients with stable cardiovascular disease.[320]

Recurrent ischemic stroke or TIA will never be eradicated, but with preventive measures focusing on known and future risk factors, as well as evolution of more effective preventive therapies, more patients will have a hope of a good life quality even after ischemic stroke.

Strengths and limitations of the thesis

Our studies have several limitations. Firstly, all papers included in this thesis are registry-based and the information in our registry as well as most other registries is gathered without any specific hypothesis in mind. Furthermore, regular medical electronic records data are not intended for research, and may thus be more prone to error and misclassification. The acquired data may also be insufficient to answer all the relevant scientific questions in a study and the analyses may thus be subject to unmeasured confounding. E.g. we have no information about the patient's adherence to secondary prevention therapies or risk factor burden in-between the admissions. Secondly, the NORSTROKE study is single-center and hospital based, and mainly covers a Caucasian population. Thus, our results may not be applicable to other demographics. Thirdly, patients are not followed as close as in a clinical study which means that recurrent events may be underestimated. Since hospitalization to specific hospitals was necessary for recurrent event identification, clinical events that were admitted to hospitals outside of Western Norway or even not hospitalized at all, were not identified. This may underestimate our recurrence rates. In our experience, not all strokes in patients with poor functional status that live in nursing homes are hospitalized. This may also be the case with patients already on maximum secondary prevention, or patients with end-stage cancer. Since we have no information about cause-specific-mortality, death of ischemic stroke without a hospital admission (e.g. patients living alone who were not able to alert the medical services) would also not be identified as recurrence in our study.

One of the main strengths of our studies is decades of electronic medical records manually accessed and collected for each patient. This ensures more precise and diverse information than automatically mined data like administrative codes used for research. Because all acute stroke in Norway is treated in the public health system, this may reduce selection bias and make the present data better transferrable to a general population. Moreover, identification of new clinical events that led to

hospitalization could be ensured for a large geographical area by the use of electronic records. Lastly, comprehensive data on medications for each patient is often not available in non-clinical studies. Thus, assessment of secondary prevention therapies in a hospital-based population gives real-life data which is an important supplement to clinical trials.

Conclusions

In this thesis, we have demonstrated modest rates of clinical recurrent ischemic stroke or TIA in our hospital-based population, both short- and long term, compared with most other previously studied populations. The risk of recurrence was highest shortly after ischemic stroke or TIA and remained elevated for the first 1.5 years after the event, with subsequent stabilization. Being admitted to a hospital with a stroke mimic was almost twice as common as suffering a recurrent ischemic stroke or TIA in the same time-period. The risk of stroke mimics was also highest early after index ischemic stroke or TIA. Patients admitted to a hospital with suspected stroke were more likely to have a stroke mimic than recurrent ischemic stroke or TIA, especially the first two years after the index event.

The risk of early recurrence among stroke subtypes was highest for patients with ischemic stroke or TIA due to stroke of other etiology (SOE) and large-artery-atherosclerosis (LAA). In the former category, most patients had malignancies as the cause of their early recurrent ischemic stroke or TIA. We found no association between the risk of long-term-recurrence and stroke subtype.

Known cardiovascular risk factors were associated with recurrent ischemic stroke or TIA. For 30-day recurrence, patients with a history of peripheral artery disease were more likely to suffer an early recurrent ischemic stroke or TIA. For long-term recurrence, patients with a history of hypertension, prior symptomatic ischemic stroke or TIA and visible chronic infarcts on MRI were more likely to experience a recurrent ischemic stroke or TIA.

About one third of our cohort died during follow-up. Suffering a recurrent ischemic stroke or TIA more than doubled the mortality risk.
We demonstrated that stroke mimics were common after suffering an ischemic stroke or TIA. The etiologies behind these stroke mimics were diverse and similar to

etiologies in patients with stroke mimics without prior ischemic stroke or TIA. The most common stroke mimic diagnoses were unspecific, especially early after index.

Appendix

1. Norwegian Stroke Research Registry Inclusion Form Excerpt

   Page 16-17: Patient data on comorbidities and discharge location

   Page 19: Patient data on medications at index event admission and discharge

Bakgrunnsopplysninger – tidligere sykdom

Tidligere cerebrovaskulær sykdom

	Ja	Nei	Ukjent	Antall	Debutår	Måned / år for siste
«Hjerneslag»	☐	☐	☐			
Hjerneinfarkt	☐	☐	☐	☐	☐☐	☐☐/☐☐
Hjerneblødning	☐	☐	☐	☐	☐☐	☐☐/☐☐
Uspesifisert	☐	☐	☐	☐	☐☐	☐☐/☐☐
TIA	☐	☐	☐	☐	☐☐	☐☐/☐☐

TIA siste 24 timer?	Klokkeslett	☐☐:☐☐
Siste uke	Dato	☐☐/☐☐/☐☐
1-4 uker før slaget	Dato	☐☐/☐☐/☐☐
4-12 uker før slaget	Dato	☐☐/☐☐/☐☐
>12 uker før slaget	Dato	☐☐/☐☐/☐☐

Tidligere sykdommer

	Ja	Nei	Ukjent	Debutår
NHR: Gjennomgått store hjerte-/ karintervensjoner?	☐	☐	☐	
Hjerteinfarkt	☐	☐	☐	☐☐
Angina pectoris	☐	☐		☐☐
Koronar intervensjon *	☐	☐	☐	☐☐
Aortaventil *	☐	☐		☐☐
Annen hjertesykdom	☐	☐		☐☐
Carotisstenose	☐	☐		☐☐
Carotisoperasjon/stent *	☐	☐	☐	☐☐
Perifer karsykdom / inkl. aorta	☐	☐		☐☐
Perifer karkirurgi/intervensjon *	☐	☐	☐	☐☐
Lungeemboli	☐	☐		☐☐
Dyp venetrombose	☐	☐		☐☐
Hypertensjon	☐	☐	☐	☐☐
Diabetes mellitus	☐	☐	☐	☐☐
Dyslipidemi	☐	☐	☐	☐☐
Atrieflimmer – paroksystisk	☐	☐	☐	☐☐
Atrieflimmer – kronisk	☐	☐	☐	☐☐
Migrene	☐	☐		☐☐
Demens	☐	☐		☐☐
Depresjon (medikamentelt behandlet)	☐	☐		☐☐
KOLS (kronisk obstruktiv lungesykdom)	☐	☐		☐☐
Cancer	☐	☐		☐☐

*** Hvis karintervensjon**	Ja
Innen siste uke	☐
1-4 uker før slaget	☐
4-12 uker før slaget	☐
>12 uker før slaget	☐

Lungecancer	☐
Brystcancer	☐
Gastrointestinal cance	☐
Urogenital cancer	☐
➔ Annen cancer	☐

Bakgrunnsopplysninger – før sykehusinnleggelsen

Røykevaner

- ☐ Aldri
- ☐ Eks-røyker: Sluttet år ☐☐
- ☐ Røyker: Antall sigaretter per dag ☐☐
- ☐ Ukjent

Alkoholvaner

- ☐ Avholdende
- ☐ Alkoholmisbruk nå
- ☐ Alkoholmisbruk tidligere: Sluttet år ☐☐

Høyde og vekt

- ☐☐☐ Høyde (cm)
- ☐☐☐ Kroppsvekt (kg)

Funksjonsstatus (modifisert Rankin Scale)

☐

0 = Ingen symptomer og ingen begrensninger i dagliglivet
1 = Lette symptomer, men i stand til å utføre alle vanlige aktiviteter
2 = Begrensninger i sosiale aktiviteter, men uavhengig i ADL
3 = Har behov for noe hjelp (instrumental ADL), men kan gå uten hjelp
4 = Kan ikke gå uten hjelp, trenger hjelp i daglige aktiviteter (basic ADL)
5 = Sengeliggende, inkontinent, avhengig av kontinuerlig hjelp

Boligforhold

- ☐ Egen bolig uten hjemmesykepleie/-hjelp
- ☐ Egen bolig med hjemmesykepleie/-hjelp
- ☐ Omsorgsbolig
- ☐ Sykehjem
- ☐ Ingen fast bopel
- ☐ Bor med familie (f.eks. generasjonsbolig)
- ☐ Ukjent

Bosituasjon

- ☐ Bodde alene
- ☐ Bodde sammen med noen
- ☐ Bodde i institusjon/sykehjem
- ☐ Ukjent

Sivil status

	Ja	Nei
Gift/samboende	☐	☐
Enke/enkemann	☐	☐
Enslig	☐	☐
Ukjent	☐	

Arbeidsstatus

	Ja	Nei
I arbeid/utdanning (hel eller deltid)	☐	☐

Utdanning (høyeste fullført)

☐ Grunnskole ☐ Videregående ☐ 3 år univ./høyskole ☐ 5år univ./høyskole

Gravid

Ja ☐ Nei ☐ Trimester 1 ☐ 2 ☐ 3 ☐ Partus dato ☐☐/☐☐/☐☐

Medikamenter

Stoffgruppe: Medikament	Før slaget				Ved utreise			
	Ja	Nei	?	Dose	Ja	Nei	?	Dose
Acetylsalicylsyre:	☐	☐	☐		☐	☐	☐	
ADP-blokker:	☐	☐	☐		☐	☐	☐	
Dipyridamol:	☐	☐	☐		☐	☐	☐	
Warfarin:	☐	☐	☐		☐	☐	☐	
LMW heparin:	☐	☐	☐		☐	☐	☐	
Faktor Xa inhibitor:	☐	☐	☐		☐	☐	☐	
Trombin inhibitor:	☐	☐	☐		☐	☐	☐	
Diuretikum:	☐	☐	☐		☐	☐	☐	
ACE-hemmer:	☐	☐	☐		☐	☐	☐	
A2-antagonist:	☐	☐	☐		☐	☐	☐	
Beta-blokker:	☐	☐	☐		☐	☐	☐	
Ca-antagonist:	☐	☐	☐		☐	☐	☐	
Alfa-blokker:	☐	☐	☐		☐	☐	☐	
Statin:	☐	☐	☐		☐	☐	☐	
Annen lipidsenker:	☐	☐	☐		☐	☐	☐	
Insulin:	☐	☐	☐		☐	☐	☐	
Antidiabetikum po:	☐	☐	☐		☐	☐	☐	
Østrogener:	☐	☐	☐		☐	☐	☐	
Hormonspiral:	☐	☐	☐		☐	☐	☐	
p-pille:	☐	☐	☐		☐	☐	☐	
Nikotinerstatning:	☐	☐	☐		☐	☐	☐	
Antidepressivum:	☐	☐	☐		☐	☐	☐	
Antidemens:	☐	☐	☐		☐	☐	☐	
Thyroxin:	☐	☐	☐		☐	☐	☐	
Antiepileptikum:	☐	☐	☐		☐	☐	☐	
«Medikamentell behandling for høyt blodtrykk»	☐	☐	☐		☐	☐	☐	
	☐	☐	☐		☐	☐	☐	
	☐	☐	☐		☐	☐	☐	
	☐	☐	☐		☐	☐	☐	
	☐	☐	☐		☐	☐	☐	
	☐	☐	☐		☐	☐	☐	

Source of data

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ORIGINAL RESEARCH

WILEY Brain and Behavior Open Access

Thirty-day recurrence after ischemic stroke or TIA

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Abstract

Background: Incidence of recurrent stroke is highest within 30 days after the initial ischemic stroke (IS) or TIA, but knowledge about early recurrence is lacking. We aimed to identify etiological groups with highest risk of early recurrence and assess how the TOAST classification identified index stroke etiology.

Methods: Medical records of 1874 IS and TIA patients in the Bergen NORSTROKE registry were retrospectively reviewed for identification of recurrent IS or TIA within 30 days after index IS or TIA. Stroke etiology was determined by review of electronical medical journals. Logistic regression was used to calculate odds ratios (OR) for 30-day recurrence.

Results: Thirty-three patients (1.8%) were readmitted with recurrent IS or TIA within 30 days after index stroke. By using TOAST, 12 patients were initially classified with stroke of unknown etiology (SUE). Etiologies behind recurrent IS or TIA were after the recurrent episode identified as extracranial large artery atherosclerosis (LAA) in 14 patients (42.4%), intracranial arterial pathology in seven patients (21.2%), active malignancy in six patients (18.2%), and cardio embolism in four patients (12.1%). Small vessel occlusion and SUE were the causes in one patient each. Logistic regression showed that patients with stroke of other determined etiology (SOE) and LAA had increased risk of 30-day recurrence (OR = 9.72, 95% CI 1.84–51.3, $p < 0.01$ and OR = 4.36, 95% CI 2.01–9.47, $p < 0.01$, respectively).

Conclusion: Patients with LAA and SOE had increased risk of recurrent IS or TIA within 30 days. TOAST was inadequate at identifying exact etiologies behind recurrent stroke at index event.

KEYWORDS

cerebrovascular disease, ischemic stroke, readmission, stroke etiology, stroke recurrence

1 | INTRODUCTION

The purpose of diagnostic evaluation of acute stroke is identification of the causal etiology behind it, in order to reduce the risk of further strokes with appropriate secondary prevention. Recurrent stroke is associated with increased disability and mortality compared to the index stroke (Petty et al., 1998; Sacco, Wolf, Kannel, & McNamara, 1982). And even with appropriate prevention, the risk of recurrence after ischemic stroke (IS) and transient ischemic attack (TIA) is high, especially in the early phase after stroke (Lovett, Coull, & Rothwell, 2004; Sacco, Shi, Zamanillo, & Kargman, 1994). Paradoxically, many large studies on recurrent stroke incidence have excluded events

occurring within the first month leaving a lack of data regarding early recurrence (Coull & Rothwell, 2004). Studies on 30-day recurrence are scarce and use varying definitions of recurring events. A meta-analysis found a pooled cumulative risk of 3.1% for 30-day recurrence, but risk estimates of 30-day recurrence vary greatly (Mohan et al., 2011). Moreover, when classifying etiology by TOAST, around 40% of patients will end up with an undetermined or cryptogenic etiology when an apparent cause is lacking or identification of multiple competing etiologies (Hart et al., 2014). Most recurrent IS is of the same type as the index episode, except for lacunar IS, which seems especially true for early recurrence (Jones, Sen, Lakshminarayan, & Rosamond, 2013; Yamamoto & Bogousslavsky, 1998). This implicates that patients with the highest risk of early recurrence may not obtain a specific etiology and thus not receive the most effective secondary prevention. A better understanding of causes behind early recurrence is therefore of utmost importance, as it may optimize prevention and thereby reduce morbidity and mortality.

We aimed to determine the etiology in patients rehospitalized with recurrent IS or TIA within 30 days after index stroke onset. We also aimed to identify etiological groups with the highest risk of early recurrence and see how TOAST identified the etiologies at index.

2 | METHODS

All patients older than 18 years of age admitted with IS or TIA to the stroke unit at the Department of Neurology, Haukeland University Hospital, between July 1, 2007, and December 31, 2013, were registered in the Bergen NORSTROKE registry. IS was defined as an episode of neurologic deficit lasting >24 hr where magnetic resonance imaging (MRI) or computed tomography (CT) showed infarctions related to the clinical findings (Johnson et al., 1995). TIA was defined as a clinical diagnosis of transient focal cerebral dysfunction lasting shorter than 24 hr with no objective evidence of brain infarction on imaging (Johnson et al., 1995). All patients were investigated with brain imaging (CT and/or MRI), carotid ultrasound, and 24-hr electrocardiographic monitoring. Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria was used for etiology classification. TOAST classifies stroke as caused by large-artery atherosclerosis (LAA), cardio embolism (CE), small vessel occlusion (SVO), other determined cause (SOE), or stroke of undetermined cause (SUE; Adams et al., 1993).

Recurrent IS or TIA was identified by review of electronic medical records from Haukeland University Hospital unit and the other eight hospitals under the Western Norway Regional Health Authority, up to 30 days after completing evaluation and being discharged alive following the index IS or TIA from our stroke unit. New focal episodes from the same arterial territory during the initial hospitalization were considered as progression of acute stroke and not recurrence. We excluded patients who died before discharge and patients discharged to palliative care. We did also not include intracerebral hemorrhage or subarachnoid hemorrhage as recurrence. TOAST etiology for the index IS or TIA was obtained from the Bergen NORSTROKE registry. Intracranial lesions were studied separately because it is challenging to discriminate between embolic and atherosclerotic intracranial arterial pathology, especially in the early phase after the initial stroke (Lee, Oh, Bang, Joo, & Huh, 2004).

After the recurrent IS or TIA, a new etiological evaluation by review of supplemental clinical and imaging data was performed by two doctors with experience in stroke medicine (ANK and HN). A possible common cause for both episodes was determined.

The study was approved by the Western Regional Ethics Committee with written informed consent obtained from all patients or their legally authorized representatives.

2.1 | Statistics

Chi-squared test was used to assess baseline characteristics for categorical variables. Students' *t* test or Mann–Whitney's *U* test was used to investigate continuous variables and expressed as mean with standard deviation (*SD*) or as median with interquartile range (IQR) if skewed. Backward stepwise regression was used to investigate the significant factors associated with 30-day recurrence. Stata/SE 15.1 (Stata Corp LLC) were used for the analyses.

3 | RESULTS

We identified 1874 patients who were discharged alive from our stroke unit after their index IS or TIA during the inclusion period, of whom 1668 with IS and 206 with TIA. CE was the most frequently determined cause of IS or TIA (*n* = 604, 32.3%), followed by LAA (*N* = 245, 13.0%), SVO (*N* = 205, 10.9%) and SOE (*N* = 32, 1.7%) during index admission. An etiology could not be determined in 42.1% of the patients.

A total of 33 patients, 28 with IS and five with TIA, (1.8%) were readmitted within 30 days after index stroke onset. Baseline characteristics are shown in Table 1. Patients with recurrence more frequently had a history of peripheral artery disease, carotid endarterectomy, a shorter length of stay (LOS) and were more often discharged home without assistance after the index event. There were no differences in age, gender, mRS at discharge, NIHSS score on admission, or treatment with IV thrombolysis between patients with 30-day recurrent IS or TIA and patients with no recurrent stroke. Five patients that experienced new focal episodes from the same vascular territory during index admission, along with two patients that suffered early recurrence with hemorrhagic stroke, were excluded from the recurrence group.

Etiology as classified by the TOAST classification after the index event is shown in Table 1. LAA was the most frequent index etiology in patients with 30-day recurrence (*n* = 14), followed by intracranial vascular lesions (*n* = 8), CE (*n* = 5), SOE (*n* = 2), SVO (*n* = 1), and SUE (*n* = 12). Median time from index stroke to recurrence was 14 days (IQR 9, 20). No patient had TIA at both events. Ten patients self-reported previous TIA symptoms. An MRI was performed in 29 of 33

TABLE 1 Baseline characteristics of population

Characteristics	30-day recurrence *N* = 33	No 30-day recurrence *N* = 1841	*p*
Age (years) mean ± *SD*	74.4 ± 11.5	73.2 ± 13.6	0.63
Sex (male)	17 (51.5)	1,019 (55.4)	0.66
mRS score, median (IQR)	1 (0, 2)	2 (0, 3)	0.06
NIHSS score, median (IQR)	1 (0, 4.5)	2 (1, 5)	0.09
BI score, median (IQR)	100 (100, 100)	100 (70, 100)	0.02
Index etiology (TOAST)			<0.01
Atherosclerosis	13 (39.4)	232 (12.6)	<0.01
Cardioembolism	5 (15.5)	599 (32.5)	0.03
Small vessel disease	1 (3.0)	204 (11.1)	0.14
Other determined	2 (6.1)	30 (1.6)	0.05
Undetermined	12 (36.6)	776 (42.2)	0.52
Comorbidities			
Peripheral artery disease	7 (21.2)	129 (7.0)	<0.01
Diabetes	6 (18.2)	275 (14.9)	0.61
Angina pectoris	3 (9.1.4)	256 (13.9)	0.43
Myocardial infarction	4 (12.1)	265 (14.4)	0.71
Hypertension	23 (69.7)	1,031 (56.0)	0.12
Atrial fibrillation	8 (18.2)	318 (18.4)	0.89
Prior/current smoking	21 (63.6)	1,066 (57.9)	0.39
Treatment			
IV thrombolysis	7 (21.2)	299 (16.2)	0.44
Carotid endarterectomy	5 (15.2)	64 (3.5)	<0.01
Length of index admission, median (IQR)	5 (2, 7)	6 (3, 10)	0.01
Discharged to			0.01
Home	22 (66.7)	985 (53.7)	0.13
Home nursing	2 (6.1)	193 (10.5)	0.41
Rehabilitation	0	152 (8.3)	0.09
Nursing home	5 (15.2)	444 (24.2)	0.23
Other department	4 (12.1)	59 (3.2)	<0.01

Note. BI, Barthel Index; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; *SD*, standard deviation.
Data are expressed as *n* (%) unless specified.

patients at both index and recurrent event. Two patients had no MRI performed at any event.

After evaluating new clinical, radiological, and other investigative data after the recurrent event, specific etiology causing both index and recurrent IS or TIA could be identified in all but one patient (Table 2). Recurring stroke made a more specific classification in all except one patient with SUE from the index event possible. LAA of extracranial arteries was considered cause of both index and recurrent stroke in 14 patients (42.4%) instead of 13 at index. Six patients had experienced TIA symptoms previous to index admission. Eleven of 14 patients had a carotid stenosis >50% ipsilateral to the affected hemisphere. Five of 11 patients underwent carotid endarterectomy (CEA), four of them after the second stroke, and one after the first, with a median time from index stroke to surgery of 12 days (IQR 8, 12). In one patient, an intima flap following CEA occluded the carotid artery causing a new IS within 30 days after index.

Seven patients (21.2%) had intracranial vascular lesions responsible for recurrent stroke in the same vascular territory: three with stenosis of the middle cerebral artery (MCA), two with intracranial carotid stenosis, one advanced intracranial atherosclerosis, and one with an MCA aneurysm.

Six patients (18.2%) had recurrent IS or TIA because of hypercoagulability caused by underlying active cancer. Only one patient was recognized as having cancer-related stroke and classified as SOE at index event. Three were classified as CE and two as SUE.

Atrial fibrillation was the final cause of stroke in four patients (12.1%) instead of five classified at index. Two patients classified as CE at index were diagnosed with cancer-associated stroke at

TABLE 2 Specific etiologies for patients after recurrence

Total (*n* = 33)	0–30 days	%
Readmitted patients, total	33	
Large-artery atherosclerosis (LAA)	14	42.4
Intracranial pathology	7	21.2
Cardioembolism (CE)	4	12.1
Small vessel occlusion (SVO)	1	3
Other demonstrated cause (SOE)	6	18.2
Stroke of unknown etiology (SUE)	1	3

TABLE 3 Logistic regression analysis with 30-day recurrence as dependent variable

	Odds Ratio	95% CI	*p*
Age, year	1.01	0.98–1.04	0.53
Female	1.39	0.66–2.95	0.38
NIHSS at admittance	0.99	0.91–1.08	0.87
Length of stay >6 days	0.90	0.82–0.99	0.03
LAA	4.36	2.01–9.47	<0.01
SOC	9.72	1.84–51.30	<0.01
Peripheral artery disease	2.61	1.03–6.60	0.04

Note. LAA, Large artery atherosclerosis; mRS, modified Rankin Scale; SOC, Stroke of other demonstrated cause; tPA, tissue plasminogen activator (intravenous thrombolysis).

recurrence. Of three CE patients, two patients were prescribed anticoagulants after the index event and one after the second event.

Small vessel occlusion was the cause of recurrent stroke in one patient. Table 3 shows results from the logistic regression analyses where 30-day recurrence vs. no 30-day recurrence is the dependent variable. IS or TIA due to SOE and LAA had significantly increased risk of 30-day recurrence compared to other etiologies, (HR = 9.72, 95% CI 1.84–51.3, $p < 0.01$ and HR = 4.36, 95% CI 2.01–9.47, $p < 0.01$, respectively). Patients with a longer length of stay ≥6 days or peripheral artery disease also had significantly higher risk of 30-day recurrence.

4 | DISCUSSION

We found that 1.8% of our patients was readmitted with a recurrent IS or TIA within 30 days. There is scant information on stroke recurrence in Norway, but our rate is low compared to many large international incidence studies (Bravata, Ho, Meehan, Brass, & Concato, 2007; Lovett et al., 2004; Sacco et al., 1994; Smith, Frytak, Liou, & Finch, 2005). Most of these studies included patients dating several decades back. Since then, improved secondary prevention may have reduced incidence of recurrent stroke and other vascular events (Hong, Yegiaian, Lee, Lee, & Saver, 2011). Our low 30-day recurrence rate may reflect this progress in stroke medicine. Another explanation might be different definitions of recurrence.

Large artery atherosclerosis had the highest risk of 30-day recurrence in our study, as previously reported by other studies (Lovett et al., 2004; Petty et al., 2000; Sacco, 1997). Considering that CEA is highly effective for reducing recurrent stroke in selected patients with stenosis of the internal carotid artery (Rothwell et al., 2003), knowing the risk of early recurrence is important for the stroke clinician in order to select and time patients for surgery. This is well illustrated in our study, as four of five patients in our study found eligible for CEA, suffered a recurrent stroke before surgery. On the other hand, peri- and postoperative complications after CEA may happen, as one patient in our study suffered a recurrent stroke due to a postoperative intimal flap. Patients with atherosclerotic lesions affecting extracranial arteries supplying the brain other than the internal carotid are also susceptible to atherosclerotic and occlusive disease causing recurrent stroke, but these patients have no proven benefit of surgical intervention. TOAST criteria require an intra- or extracranial stenosis of >50% to classify a stroke as LAA, a criterion originating from the NASCET study in which carotid stenoses were graded from angiograms (North American Symptomatic Carotid Endarterectomy Trial Collaborators et al., 1991). Since then, growing evidence shows that even in nonstenotic intra- or extracranial arteries, high-risk atherosclerotic plaques may be the culprit of IS or TIA due to artery-to-artery embolization (Brinjikji et al., 2016; Kim & Kim, 2014). These cases nevertheless often end up being classified as cryptogenic, which may explain why patients with LAA in our study were initially classified as SUE, as more modern imaging techniques like emboli detection monitoring and contrast-enhanced ultrasound were not routine practice in our stroke unit in the study period.

In our study, a significant part of patients with recurrence had intracranial vascular lesions causing recurrent IS or TIA. Intracranial stenosis is less common in a more Caucasian population as ours, but still has a high risk of causing recurrent stroke (Holmstedt, Turan, & Chimowitz, 2013). As intracranial vessels may become stenotic or occluded due to both atherosclerotic and embolic disease, we did not etiologically group them as LAA, but as a separate group. Spontaneous recanalization of emboli in the intracranial arteries will often occur, but may happen both in the acute phase and days and weeks after the initial stroke (Rha & Saver, 2007). As a result of this, it may be difficult to discriminate between LAA and CE as cause of an intracranial lesion in the first weeks and months after stroke. All patients with intracranial etiology in our study were investigated for both extracranial atherosclerotic and cardiac pathology, and received medical therapy and risk factor management without any mechanical intervention. Patients with severe intracranial vascular pathology in our population also seem prone to early recurrence.

Active cancer was the suspected cause of both index and recurrent stroke or TIA in six (18.2%) patients. Cancer cells secrete

procoagulant factors that may induce a hypercoagulable state causing ischemic stroke and other thromboembolic complications (Bick, 2003). In clinical practice, cancer-related stroke is considered rare and difficult to diagnose (Grisold, Oberndorfer, & Struhal, 2009). In our study, several of these patients were initially classified as CE because of infarcts in multiple vascular territories. Patients with cancer-related coagulopathy may be prone to early recurrence and our findings suggest that in patients with recurrent IS or TIA within 30 days, it may be warranted to screen for a malignancy, especially in patients with embolic infarctions. Our numbers are very small though and need to be confirmed in larger studies.

Patients with CE and SVO had the lowest rate of 30-day recurrence with around 0.5% each. In other studies, early CE stroke recurrence varies between 1% and 10% (Arboix & Alio, 2010). Many of these studies were however performed before anticoagulation was implemented as standard practice. Studies investigating the effect of aspirin vs. low molecular-weight heparin in the early phase have generally shown no benefit of anticoagulation, suggesting that early re-embolization is rare (Paciaroni, Agnelli, Micheli, & Caso, 2007). Recently published data from our stroke registry show no correlation between time to MRI and frequency of multiple acute cerebral infarcts in cardio embolic IS, suggesting that cardiogenic emboli seem to happen as a shower and not successively (Novotny, Khanevski, Thomassen, Waje-Andreassen, & Naess, 2017).

SVO also is reported to have low recurrence rates (Jones et al., 2013; Lovett et al., 2004; Petty et al., 2000; Sacco, 1997). Although the exact pathology of stroke due to SVO is still under debate, the process leading to stroke is thought to be intrinsic to the small vessels (Wardlaw, 2005). This would mean that there are fewer sources of thrombus or emboli compared with non-SVO stroke. A small meta-analysis found a lower early risk of recurrence in patients with SVO compared to non-SVO stroke (Jackson et al., 2009). In our data, only one patient suffered recurrent stroke due to SVO within 30 days.

This study has some limitations. This study is not prospective and the estimation of the recurrence rate is based on patients who from our stroke unit who sought medical care and were readmitted to our stroke unit or other hospital under the Western Norway Regional Health Authority. Furthermore, the single-hospital design may cause sampling bias and reducing the number of patients with recurrent stroke, thus limiting the generalizability of our findings. However, we do not have data if patients were hospitalized in other regions of Norway or abroad. We cannot exclude that some patients may have suffered recurrent IS or TIA without a readmission to the hospital, even if we have a very low admission threshold in suspected acute stroke. On the other hand, it provides us with precise clinical data as compared to studies using administrative databases for identification of both recurrent stroke and their causes. In addition, we deviated from the TOAST classification in assessment of intracranial vascular lesions.

A strength of this study is that it investigates a general stroke population by review of medical records which gives a real-life perspective on early recurrent stroke. Our single-hospital design gives a high possibility of identifying most recurrent stroke cases that were hospitalized in our hospital or neighboring hospitals in Western Norway. Furthermore, it adds insight into patients groups not previously well studied for 30-day recurrence, such as patients with intracranial vascular lesions and cancer.

In conclusion, most recurrent early IS and TIA cases are caused by LAA of extracranial arteries and intracranial atherosclerotic or embolic disease. TOAST identified only a proportion of patients accurately at the index event. Patients with recurrent stroke that lack conventional risk factors may be considered for cancer screening.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Recurrent ischemic stroke: Incidence, predictors, and impact on mortality

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Background and purpose: Recurrent ischemic stroke (IS) or TIA is frequent with a considerable variation in incidence and mortality across populations. Current data on stroke recurrence and mortality are useful to examine trends, risk factors, and treatment effects. In this study, we calculated the incidence of recurrent IS or TIA in a hospital-based stroke population in Western Norway, investigated recurrence factors, and estimated the effect of recurrence on all-cause mortality.

Methods: This prospective cohort study registered recurrence and mortality among 1872 IS and TIA survivors admitted to the stroke unit at Haukeland University Hospital between July 2007 and December 2013. Recurrence and death until September 1, 2016, were identified by medical chart review. Cumulative incidences of recurrence were estimated with a competing risks Cox model. Multivariate Cox models were used to examine recurrence factors and mortality.

Results: During follow-up, 220 patients had 277 recurrent IS or TIAs. The cumulative recurrence rate was 5.4% at 1 year, 11.3% at 5 years, and 14.2% at the end of follow-up. Hypertension (HR = 1.65, 95% CI 1.21-2.25), prior symptomatic stroke (HR = 1.63, 95% CI 1.18-2.24), chronic infarcts on MRI (HR = 1.48, 95% CI 1.10-1.99), and age (HR 1.02/year, 95% CI 1.00-1.03) were independently associated with recurrence. A total of 668 (35.7%) patients died during follow-up. Recurrence significantly increased the all-cause mortality (HR = 2.55, 95% CI 2.04-3.18).

Conclusions: The risk of recurrent IS stroke or TIA was modest in our population and was associated with previously established risk factors. Recurrence more than doubled the all-cause mortality.

KEYWORDS
cerebrovascular disease, neuroepidemiology, stroke etiology, stroke recurrence

1 | INTRODUCTION

The incidences of stroke and post-stroke mortality have declined heavily in high-income countries in the last 50 years, mainly because of changes in cardiovascular risk factors and improvements in acute stroke treatment.[1] Despite progress and declining trends, recurrent stroke is still frequent.[2,3] Studies demonstrate varying recurrence rates, ranging from 7%-20% at 1 year to 16%-35% at 5 years.[4,5] Recurrent ischemic stroke (IS) has been associated with increased mortality and functional dependence,[6,7] but this remains insufficiently explored. The primary goal of secondary prevention strategies after IS or transient ischemic attack (TIA) is to reduce the risk of recurrent stroke, and information on stroke recurrence and survival is useful to assess the effect of secondary prevention and risk factors for recurrence and death.

In this study, we aimed to investigate the cumulative incidence of recurrent IS or TIA in a Norwegian hospital-based stroke population, as well as investigate factors associated with recurrence. We also wanted to assess the all-cause mortality after IS or TIA and the influence of recurrence on mortality.

2 | MATERIALS AND METHODS

In this hospital-based prospective cohort, all patients older than 18 years admitted with IS or TIA to the Stroke Unit at the Department of Neurology, Haukeland University Hospital, between July 1, 2007, and December 31, 2013, were prospectively registered in the Bergen NORSTROKE Registry. Approximately 275 000 people are living in the area served by our stroke unit. For this analysis, we only included patients that lived inside this area at the time of the index IS or TIA. Patients that moved outside of the defined geographic area before the end of data collection, and patients that died during index admission or were discharged to palliative care, were excluded from the analysis. Patients from our area admitted to other hospitals with index stroke were not included in the study.

Ischemic stroke was defined as an episode of neurologic deficit lasting >24 hours or clinical symptoms where magnetic resonance imaging (MRI) or computed tomography (CT) showed infarctions related to the clinical findings.[8] TIA was defined as a clinical diagnosis of transient focal cerebral dysfunction lasting <24 hours with no objective evidence of brain infarction on brain imaging. Chronic infarctions were defined as MRI findings of focal hyperintensity lesions on T2 sequences and low signal intensity in the presence of gliosis and/or cystic encephalomalacia on FLAIR sequences.[9] Differentiation from perivascular spaces and other lesions was made by a neuroradiologist or experienced stroke clinician (HN). Brain imaging (CT and/or MRI), carotid ultrasound, and 24-hour electrocardiographic monitoring were obtained during index admission. The Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria were used for etiology classification.[10] Clinical symptoms were classified with the Oxfordshire Community Stroke Project Classification (OCSP).[11] Clinical characteristics, NIHSS, mRS, comorbidity, and medical history including previous IS or TIA were registered during index admission.

Definition of recurrent IS or TIA was the same as for the index event. Clinical recurrence was identified by review of electronic medical records from all ten hospitals under the Western Norway Regional Health Authority. Information on death was collected electronically from the Norwegian National Registry. Patients were followed until September 1, 2016. Data collection was performed mainly during 2017. We did not include intracerebral hemorrhage or subarachnoid hemorrhage as recurrent events. The study was approved by the Western Regional Ethics Committee with written informed consent obtained from all patients or their legally authorized representatives.

3 | STATISTICS

Univariate analyses were performed using the chi-squared test for categorical variables and Student's *t* test or Mann-Whitney's *U* test for continuous variables. Categorical variables are presented as N (%), and continuous variables are expressed as mean ± standard deviation (SD) or as median with interquartile range (IQR) if skewed. Cumulative incidence of recurrence was calculated with the cumulative incidence function (CIF) after applying the method of Fine and Gray by treating death as a competing risk.[12] Kaplan-Meier method was used to estimate the incidence of all-cause mortality. Factors independently associated with IS or TIA recurrence were assessed with backward stepwise Cox regression by analysis of variables that turned out significant ($P < 0.05$) in the univariate analyses. The effect of recurrence on all-cause mortality was analyzed by creating a Cox regression model with recurrence as a time-dependent covariate. Known mortality-associated factors such as age, smoking, stroke severity, and risk factors for stroke were included in the model. We analyzed the data with Stata/SE 15.1 (Stata Corp LLC,).

4 | RESULTS

During the inclusion period, 1988 patients were diagnosed with IS or TIA, of whom 116 died during the index admission or were discharged to palliative care (5.8%). The final cohort consisted of 1872 patients with index IS (n = 1666) or TIA (n = 206). The mean age was 73.2 years (range 18-99 years) and 837 were women (44.7%). MRI was performed in 1629 patients (87.1%) during the index hospitalization. A total of 243 patients (13.0%) had a history of previous IS, and 144 (7%) had a history of previous TIA.

At index admission, 714 (38.1%) and 158 (8.4) patients were already on antiplatelet agents and anticoagulation agents, respectively. At index discharge, the indicated drugs were prescribed in 1228 (65.6%) and 630 (33.7%) patients. The number of patients on lipid-lowering drugs, antihypertensive drugs, and antidiabetic drugs at index admission was 537 (28.7%), 886 (47.3%), and 206 (11.0%),

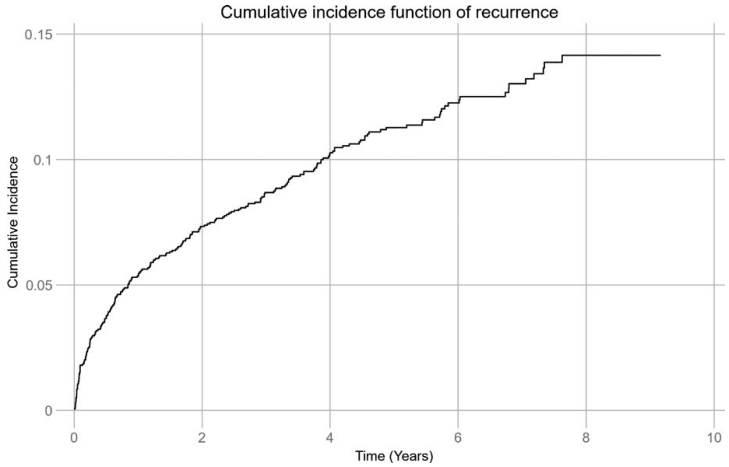

FIGURE 1 Cumulative incidence of first recurrence of ischemic stroke or TIA

respectively. At index discharge, that increased to 1331 (71.1%), 1178 (62.9%), and 247 (13.2%) patients. Only 0.8% of patients (n = 14) were not assigned any secondary prevention, mainly because of contraindications. Cardioembolism was the most frequent determined etiology (n = 604, 32.3%), followed by large-artery atherosclerosis (N = 244, 13.0%), small vessel occlusion (N = 205, 11.0%), and stroke of other determined etiology (N = 32, 1.7%). In 787 patients (42.1%), an etiology could not be determined. Partial anterior circulation infarct (PACI) was the most common clinical Oxfordshire subtype at index (n = 882, 47.3%).

During a mean follow-up of 5.6 years (median 5.5 years, max. 9.2 years, 8172.8 person-years), 220 (11.7%) patients experienced 241 (87%) recurrent IS and 36 (13%) TIA. One recurrent event was observed in 175 patients, two in 36 patients, three in six patients, and four in three patients. First recurrence was IS in 195 (88.6%) patients and TIA in 25 (11.4%) patients. Median time to the first recurrence was 436.5 days. Figure 1 demonstrates the cumulative incidence function adjusted for age (CIF) of recurrent IS and TIA. The total cumulative recurrence rate adjusted for age during follow-up was 14.2%. After 1 year and 5 years, recurrence was observed in 101 (5.4%) and 201 (10.7%) patients, respectively, resulting in age-adjusted cumulative recurrence of 5.4% and 11.3% at 1 year and 5 years, respectively. The total incidence rate per 1000 person-years during follow-up was 34.0 (95% CI 30.2-38.2), being the highest the first year with 67.8 recurrences (95% CI 56.6-81.2) per 1000 person-years.

Baseline characteristics of the cohort stratified by recurrence status at the end of follow-up are presented in Table 1. Patients with recurrence had a significantly lower discharge mRS score, more frequently a history of previous IS or TIA as well as chronic infarcts seen on MRI, a history of hypertension, and was more frequently prescribed antiplatelet agents and antihypertensive drugs at index admission.

Table 2 shows factors independently associated with recurrence from the final Cox regression model. History of hypertension at index admission was the strongest independent risk factor, with a 65% increased risk for recurrence. Previous symptomatic cerebrovascular disease was associated with a 63% higher risk of recurrence, while chronic infarcts seen on MRI at index admission increased the risk with 48%. Older age increased the risk of recurrence with 2% per year. There were no differences between patients treated with antiplatelet agents or anticoagulants.

A total of 668 (35.7%) patients died during follow-up. Of the 220 patients with recurrence, 96 (43.6%) died, whereas 572 (34.6%) of the 1652 patients without recurrence died ($P < 0.01$). Kaplan-Meier estimates representing the risk of all-cause death after stroke are demonstrated in Figure 2. Total cumulative incidence of all-cause death during follow-up was 51.2%, varying from 47.4% in patients with no recurrence to 57.8% in patients with recurrence. The cumulative risk of all-cause death at 1 and 5 years was 10.7% and 33.5%, respectively. Factors independently associated with mortality are presented in Table 3. Recurrent IS or TIA was the strongest risk factor for death, with a 2.5-fold increase in the all-cause mortality adjusted for known factors independently increasing the risk of death such as smoking, diabetes, coronary artery disease, older age, and stroke severity at discharge. When we excluded the 25 patients with TIA as the first recurrent event from the mortality analysis, a 2.6-fold increase in the risk of death in patients with recurrent IS was found. Patients treated with statins for high cholesterol had a lower risk of death.

5 | DISCUSSION/CONCLUSION

In this prospective cohort study, the cumulative incidence of clinical recurrent IS or TIA was 5.4% at 1 year and 11.3% at 5 years. This is

TABLE 1 Baseline characteristics at index stroke (N, %)

	No recurrence	Recurrence	
	N = 1652	N = 220	*P*
Age (y), mean ± SD	73.0 ± 13.8	75.0 ± 11.3	0.07
Male sex	917 (55.5)	118 (53.6)	0.60
mRS score at index discharge, median (IQR)	2 (1, 3)	1 (0, 3)	0.03
NIHSS score at admission, median (IQR)	2 (1, 5)	2 (0, 5)	0.20
Stroke diagnosis at index			
Ischemic stroke	1468 (88.9)	198 (90.0)	0.61
TIA	184 (11.1)	22 (10.0)	0.61
TOAST subtype at index			
Large-artery atherosclerosis	207 (12.5)	37 (16.8)	0.08
Cardioembolism	537 (32.5)	67 (30.4)	0.54
Small vessel occlusion	187 (11.3)	18 (8.2)	0.16
Other determined etiology	27 (1.6)	5 (2.3)	0.49
Undetermined etiology	694 (42.0)	93 (42.3)	0.94
OCSP classification			
TACI	164 (10.0)	15 (6.9)	0.15
PACI	771 (48.9)	111 (50.9)	0.26
POCI	322 (19.6)	46 (21.1)	0.60
LACI	388 (23.6)	46 (21.1)	0.42
Comorbidities prior to index event			
Prior ischemic stroke	199 (12.1)	44 (20.0)	<0.01
Prior TIA	116 (7.0)	28 (12.7)	<0.01
Peripheral artery disease	117 (7.1)	19 (8.6)	0.40
Coronary artery disease	367 (22.2)	51 (23.2)	0.75
Diabetes mellitus	240 (14.5)	41 (18.6)	0.11
Atrial fibrillation	476 (28.8)	67 (30.5)	0.61
Hypertension	902 (54.6)	150 (68.2)	<0.01
Ever-smoker	956 (57.8)	130 (59.1)	0.73
Length of stay, median (IQR)	6 (3, 10)	5 (3, 8)	0.17
Type of prophylaxis at index discharge			
Antiplatelet agent	1069 (64.7)	159 (72.2)	0.03
Anticoagulation agent	570 (34.5)	60 (27.3)	0.03
No prophylaxis	13 (0.8)	1 (0.5)	0.45
Silent infarcts seen on MRI at index	466 (32.5)	85 (43.8)	<0.01
Other medications at index discharge			
Statins and other lipid-lowering drugs	1174 (71.1)	157 (71.4)	0.93
Antihypertensive drugs	1025 (62.1)	153 (69.6)	0.03
Antidiabetic drugs	209 (12.5)	38 (17.3)	0.06

Abbreviations: IQR, interquartile range; LACI, lacunar infarct; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PACI, partial anterior circulation infarct; POCI, posterior circulation infarct; TACI, total anterior circulation infarct.

TABLE 2 Factors associated with recurrence after IS or TIA, (n = 1621)

	HR	95% CI	P
Age, y	1.02	1.00-1.03	0.01
Female	0.99	0.74-1.33	0.96
mRS score	0.91	0.82-1.01	0.07
History of IS or TIA	1.63	1.18-2.24	<0.01
History of hypertension	1.65	1.21-2.25	<0.01
Chronic infarcts seen on MRI at index	1.48	1.10-1.99	0.01

Abbreviations: HR, hazard ratio; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

considerably lower compared with a meta-analysis from 2011, which estimated a pooled cumulative risk of 11.1% at 1 year and 26.4% at 5 years.[4] One explanation for this difference could be the declining incidences of stroke recurrence, which have been observed in studies on temporal trends of recurrence.[2,3] Furthermore, optimal use of secondary prevention strategies has shown a significant reduction in the absolute risk of recurrence.[13] Almost all patients in our study were prescribed antiplatelet or anticoagulant treatment, and the use of statins and antihypertensive treatment was high compared to other studies.[14] Finally, differences in populations, methods, and use of statistical analyses in studies on recurrence make comparison between them difficult. The Kaplan-Meier survival analysis may overestimate the cumulative incidence of recurrence since death is not treated as a competing risk.[15] Recent studies adjusting for competing risk of death have reported 1- and 5-year incidences of recurrence of 3.6%-7.7% and 10.1%-16.8%.[16-19] Our results are thus supporting newer data from several other populations.

Among the factors associated with recurrence in our study, previous hypertension at index stroke was the strongest one. Hypertension is usually considered the single most important risk factor for first stroke, but its role in the risk of recurrence is uncertain. Some studies have reported this association,[7,20] while other studies have found diabetes, coronary heart disease, and atrial fibrillation as the strongest risk factors.[21,22] Neither of these were independently associated with recurrence in our study and did not differ between patients with or without recurrence (Table 1). No single factor has been consistently associated with recurrent IS or TIA.[21] Case mix, changes in risk factor profiles, and risk factor control may affect the significance of independent factors over time and influence the results of individual studies.

In our cohort, we studied a general hospital-based stroke population for recurrence and included patients with a history of IS or TIA thus making the results relevant for clinical practice. Both previous IS or TIA and chronic infarcts on MRI were independently associated with a higher risk of recurrent stroke. Although some studies use the concept of "first stroke" as index event, we chose to include patients with prior stroke at index IS or TIA in this study. While 19.2% of the patients in this study had a history of prior clinical IS or TIA, almost

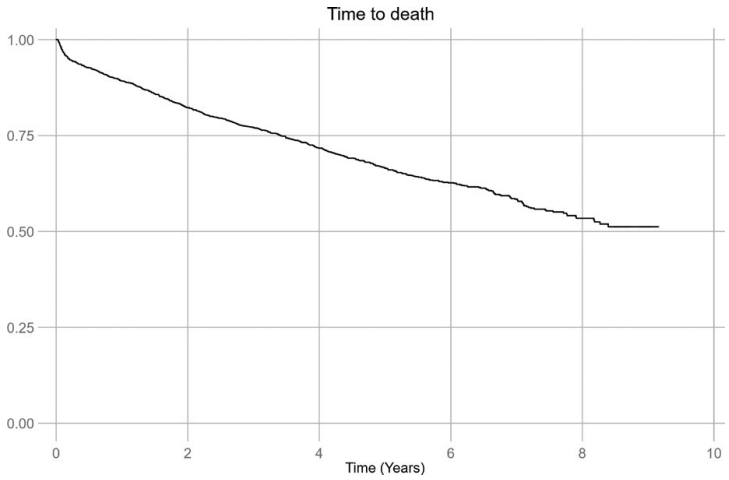

FIGURE 2 Time do death after index ischemic stroke or TIA

twice as many (33.8%) had chronic infarcts visible at MRI during index IS or TIA. In a recent meta-analysis, chronic brain infarction at index IS or TIA doubled the risk of recurrent stroke, which is similar to our results.[23]

Recurrent ischemic stroke or TIA was a strong independent factor doubling the mortality risk in our cohort. Despite the overall high incidence of recurrent stroke, few studies have investigated the impact of recurrence on all-cause mortality. Studies have reported unadjusted estimates ranging from a 2-fold increase in mortality to a 17-fold increase.[7,24] However, two other studies using similar statistical approaches as in our study reported adjusted relative mortality risks of 2.7 and 3.0 after recurrence,[6,25] which are more similar to our findings. The mechanisms behind how recurrence affects mortality are not well studied. Stroke severity is considered the most significant factor influencing short- and long-term outcome after stroke,[26] and when recurrent stroke adds to existing neurological deficit, patients may be more prone to complications and a worse outcome. One study found that a contralateral recurrent stroke led to more severe functional disability than patients with ipsilateral recurrence, which reduces the brain's ability to compensate.[7]

TABLE 3 Impact of recurrence on all-cause mortality after IS or TIA, (n = 1854)

	HR	95% CI	*P*
Recurrent stroke	2.55	2.04-3.18	<0.01
Age, y	1.09	1.08-1.10	<0.01
Female	0.85	0.72-1.00	0.06
NIHSS at discharge	1.08	1.07-1.10	<0.01
History of coronary artery disease	1.22	1.03-1.45	0.02
History of diabetes	1.48	1.21-1.80	<0.01
Previous or current smoking at index	1.47	1.24-1.74	<0.01
Statins and other lipid-lowering drugs at index discharge	0.81	0.69-0.96	0.02

Abbreviations: HR, hazard ratio; NIHSS, National Institutes of Health Stroke Scale.

Our study has limitations. First, we may have underestimated the true incidence of recurrence, as recurrent events were identified by review of medical records, and thus patients had to be admitted to a hospital within our region to be included as a recurrent event. Furthermore, we have no data on drug compliance and scarce data on cause of death, which limits the interpretation of factors affecting mortality. Finally, the findings from our Caucasian population with mostly mild IS or TIA and high rates of secondary prevention may not be transferable to other demographics.

The main strength of this study is that we have obtained high-quality 1- and 5-year recurrence and mortality data in a hospital-based stroke population. A predefined investigation protocol and the use of electronic medical records for identification of recurrent IS or TIA provide precise and accurate clinical data on both index event and on the recurrent episode as compared to studies using administrative data. All ischemic stroke cases were confirmed with imaging studies. On this background, we conclude that the risk of recurrent IS or TIA is modest in our population and that recurrent stroke has a high negative impact on all-cause mortality.

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None.

CONFLICT OF INTEREST

None.

DATA AVAILABILITY

The anonymized data that support the findings of this study are available on request from the first author, ANK. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

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