Hospital readmission after ischemic stroke or TIA

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List of abbreviations

AED: antiepileptic drugs
AHA: American heart association
ASA: American stroke association
ASCO: Acronym for a stroke etiology classification system:
Atherosclerosis, Small-vessel disease, Cardiac source, Other cause
BI: Barthel Index
CCS: Causative Classification System
CE: Cardioembolism
CI: Confidence interval
CISS: Chinese Ischemic Stroke Subclassification
CNS: Cerebral nervous system
COPD: Chronic obstructive pulmonary disease
CT: computed tomography
CTA: computed tomography with angiography
DVT: deep vein thrombosis
DWI: diffusion weighted imaging'
ECG: Electrocardiography
GI: gastrointestinal
HR: Hazard ratio
LAA: Large artery atherosclerosis
MRI: magnetic resonance imaging
mRS: modified Rankin Scale
NIHSS: National Institute of Health Stroke Scale
OR: Odds ratio
SOE: Stroke of other determined etiology
SSS-TOAST: Acronym for a stroke etiology classification system:
Stop Stroke Study – Trial of ORG 10172 in Acute Stroke Treatment
SUE: Stroke of undetermined etiology
SVO: Small vessel occlusion
TIA: Transient ischemic attack
TOAST: Trial of ORG 10172 in Acute Stroke Treatment
UTI: Urinary tract infection
VTE: venous thromboembolism

Contents

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Abstract

Background

Considerable advances in the field of stroke medicine have led to declining trends in stroke incidence, disability, and mortality in the Western world. Despite this, the absolute number of people affected by stroke has increased. The majority of stroke patients in Norway are 75 years or older. With increasing numbers of stroke survivors and an aging population, stroke represents a major challenge to healthcare systems and public health. Complications and readmissions are frequent after stroke and lead to increased morbidity, mortality and health care costs. Readmission is also considered a quality-metric for health care services. Studies on which subgroups of Norwegian stroke patients that are at highest risk of readmission have not been performed in Norway. Further knowledge on the causes of readmission and which subgroups of stroke patients that are at highest risk for readmission is important, as it may help avoid preventable readmissions after stroke.

Methods and materials

The thesis is based on studies I-IV, in which data from the Norwegian Stroke Research Registry (NORSTROKE) have been used. For the present studies, all 1874 surviving patients admitted with ischemic stroke or transient ischemic attack (TIA) to the stroke unit at Haukeland University Hospital between July 2007 and December 2013 have been followed by review of medical records for identification of unplanned readmissions up to five years after discharge from the stroke unit. Stroke etiology was classified according to the TOAST criteria as large-artery atherosclerosis (LAA), cardioembolism (CE), small vessel occlusion (SVO), stroke of other determined etiology (SOE), or stroke of undetermined etiology (SUE). Patients with residency outside the catchment area of Haukeland University Hospital were excluded due to difficulty on follow-up.

Results

Thirty-day readmission (Study I): The 30-day readmission rate among 1874 ischemic stroke and TIA patients was 10.7%. The most frequent cause of readmission was a stroke-related event, followed by infection, recurrent stroke/ TIA, and cardiac disease. Factors that independently increased the risk of 30-day readmission were increasing age, peripheral artery disease, enteral feeding, and LAA stroke subtype. The risks of all-cause readmission, recurrent stroke, and stroke-related events were increased in patients with LAA or SOE subtype, whereas the risk of cardiac disease was increased in patients with CE subtype. Thirty-day readmission increased the risk of one-year mortality.

Readmission within 90 days versus day 91-365 (Study II): Of 1175 ischemic stroke patients, the first unplanned readmission occurred within 90 days in 18.8% and between day 91 and 365 in 24.5%. Infections, recurrent stroke, cardiac disease, and stroke-related events were the most common causes of readmission during both periods. Increasing age, poorer functional outcome, LAA subtype, atrial fibrillation, and an increased risk factor burden were associated with 90-day readmission, whereas increasing age and prior myocardial infarction were associated with readmission between day 91 and 365. Patients readmitted within 90 days had a shorter length of stay during the index admission, a poorer physical function and higher frequencies of LAA subtype, atrial fibrillation, and complications with infections during the index admission compared to patients readmitted between day 91 and 365.

Readmission within one year versus the second and fifth year (Study III): Of the 1453 ischemic stroke and TIA patients followed for five years, 39% were readmitted within one year, whereas 53% of the patients that survived for one year without any unplanned readmissions were readmitted within five years. Peripheral artery disease was associated with readmission within one year, whereas atrial fibrillation was associated with readmission between the second and fifth year. Increasing age, poorer functional outcome, coronary artery disease, and hypertension were associated with readmission during both periods. Patients readmitted within one year were older, had more severe strokes, a poorer functional outcome, and more complications during the index

admission than patients readmitted between the second and fifth year, but they did not differ in the occurrence of cardiovascular comorbidity or prescribed medication at discharge or at the time of the first readmission.

Readmission and death within five years (Study IV): Among 1453 ischemic stroke and TIA patients, the five-year incidences of readmission and mortality were 72.6% and 34.5%, respectively. Both varied significantly between stroke subtypes, with the highest incidences in patients with CE or LAA subtype, and the lowest incidences in patients with SVO or SOE subtype. After adjusting for age, sex, mRS score, premorbid care-status, and the risk factor burden, CE subtype had a 25% higher risk of all-cause readmission and a 34% higher risk of death compared to other subtypes, whereas SVO subtype had a 21% lower risk of all-cause readmission and a 48% lower risk of death. Within five years, 30% had been readmitted due to an infection, 20% due to cardiac disease, 15% due to a stroke-related event, 14% due to recurrent stroke, and 12% due to a fracture. The incidence of readmission due to infection, cardiac disease, and fractures varied significantly among stroke subtypes, with the highest incidences of all observed in patients with CE subtype. There was no difference in the incidence of five-year recurrent stroke or stroke-related events among stroke subtypes.

Conclusions

The vast majority of ischemic stroke and TIA patients were readmitted within five years after discharge from our stroke unit, with more than one-fourth presenting during the first three months. Infections, stroke-related events, and cardiovascular events including recurrent stroke were the main contributors to readmission. Age, poor functional outcome and atherosclerosis in other territories than the cerebrovascular one, were important predictors of readmission. Our results also demonstrate that the incidence and causes of readmission vary by ischemic stroke subtype, and that readmission contributes to higher mortality in stroke patients.

List of publications

The thesis is based on the following papers

I. Bjerkreim AT, Khanevski AN, Selvik HA, Waje-Andreassen U, Thomassen L, Naess H, Logallo N.
The impact of ischaemic stroke subtype on 30-day hospital readmissions
Stroke Res Treat. 2018; 2018:7195369

II. Bjerkreim AT, Thomassen L, Brøgger J, Waje-Andreassen U, Naess H.
Causes and predictors for hospital readmission after ischemic stroke
J Stroke Cerebrovasc Dis. 2015;24:2095-2101

III. Bjerkreim AT, Naess H, Khanevski AN, Thomassen L, Waje-Andreassen U, Logallo N.
One-year versus five-year hospital readmission after ischemic stroke and TIA
BMC Neurol. 2019;19:15

IV. Bjerkreim AT, Khanevski AN, Thomassen L, Selvik HA, Waje-Andreassen U, Naess H, Logallo N.
Five-year readmission and mortality differ by ischemic stroke subtype
Under review.

Introduction

The other organs exist to keep the brain functioning normally. Any change in the brain's function and activity profoundly affects living. No medical task exists that is more complex, more multifaceted, more important, and potentially more rewarding than caring for a stroke patient.

Louis R. Caplan.

What defines us as humans and individuals, such as personality, emotions, intelligence and sense of humor, are all functions of our brains. Therefore, a stroke can be a personal tragedy, striking suddenly and without warning, causing temporary or permanent damage which can change us as humans and make us dependent on others, or even lead to death.

The traditional perception of stroke as a geriatric disease, resulting in severe disability or death has changed during the last three decades. Due to significant advances in the field of diagnostics, stroke medicine and communication, stroke is now considered as an event that may occur at any age, and further as a preventable and treatable disease with a survival rate higher than ever before. As a result, an increasing number of people are living with stroke sequela, and stroke is now the third leading cause of long-term disability in the world.[1]

A stroke can cause a ripple effect leading to other health problems. Neurological and medical complications, deterioration of established diseases, and development of new diseases occur both in the acute and chronic phase after stroke as a result of neurological impairments, reduced mobility, existing comorbidity, and side-effects from medical treatment.[2] These complications are important contributors to post-stroke morbidity and mortality, and they may cause prolonged hospitalizations and hospital readmissions.[3, 4] Stroke is regarded as one of the most common diseases

causing hospital readmissions.[4] Readmissions impose a great burden for stroke patients and their families and require a substantial amount of health care resources for a system already under high pressure on human and economic resources.

Even though stroke can occur at any age, it is mostly a disease of the elderly.[5] The life-expectancy in Norway has been steadily increasing, and in 2017, Norwegian women and men were expected to live 84 years and 81 years, respectively.[6] As a result of an aging population with a high life-expectancy and declining post-stroke mortality, the number of stroke survivors in Norway will increase. Therefore, the number of readmitted stroke patients will presumably increase, challenging the public health and health care systems tremendously.

Ischemic stroke and TIA

Definition

In 1976, the WHO defined a stroke as "rapidly developing clinical signs of focal (at times global) disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than a vascular origin".[7] Advances in neuroimaging, neuropathology and basic science led to an updated definition of stroke proposed by the Stroke Council of the American Heart Association (AHA)/American Stroke Association (ASA) in 2013, including definitions of ten conditions which should all be termed stroke.[8] Table 1 shows the definition of ischemic stroke proposed by the AHA/ASA.

For the present thesis, ischemic stroke was defined according to the Baltimore-Washington Cooperative Young Stroke Study Criteria as an episode of neurologic deficit lasting ≥24 hours with ischemic lesions on computed tomography (CT) or magnetic resonance imaging (MRI), or a clinical transient ischemic attack (TIA) where CT or MRI showed infarctions related to the clinical findings.[9] This definition is similar to the update definition from AHA/ASA.

Table 1. Definition of ischemic stroke and TIA by The American Heart Association and The American Stroke association.

Definition of CNS infarction: CNS infarction is brain, spinal cord, or retinal cell death attributable to ischemia, based on 1. Pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or 2. Clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥24 hours or until death, and other etiologies excluded.
Definition of ischemic stroke: An episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction.
Definition of TIA: a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.

Adapted from Sacco RL et al., Stroke, 2013,[8] and Easton et al., Stroke, 2009.[10] With permission from the publisher

If the neurological deficits caused by cerebral ischemia resolves without any objective evidence of brain tissue injury, the episode is called a TIA. TIA was previously defined as a sudden focal cerebral dysfunction assumed to be of vascular origin lasting <24 hours. With emerging imaging advances, studies revealed that 30% to 50% of patients with TIA according to the old definition had an acute lesion present on diffusion-weighted imaging (DWI).[10] A new definition for TIA was therefore proposed by the AHA/ASA in 2009 (Table 1).[10] The definition of TIA in the current thesis is a transient focal cerebral dysfunction lasting <24 hours with no objective evidence of brain infarction on imaging.

Epidemiology

In 2013, the worldwide incidence and prevalence of stroke were 10.3 million and 25.7 million, respectively.[1] Stroke was the third most common cause of disability, and the second most common cause of death after ischemic heart disease, accounting for almost 12% of all global deaths.[1, 11] The lifetime risk of stroke after the age of 25 years is 25%.[12] During the past four decades, the stroke incidence has decreased by 42% in high-income countries but increased more than 100% in low to middle-income countries.[13] Despite the globally declining trends in stroke incidence, prevalence, disability, and mortality, the absolute numbers of people affected by stroke and people living with disabilities because of stroke, have increased.[14] The incidence of stroke in Norway has declined from 15000 in the 1990s to 12000 in 2016.[5, 15] Still, cerebrovascular disease is the third most frequent cause of death and the fourth most frequent cause of premature death, and a common cause of disability among the elderly.[16, 17]

Ischemic stroke represents the most common type of stroke and accounts for 71% of all stroke survivors and 67% of new strokes.[1] In high-income countries, the incidence of ischemic stroke has declined by 13% from 1990 to 2010.[18] Approximately 51% of

all stroke deaths are caused by ischemic stroke. Mortality from ischemic stroke has been reduced by 37% from 1990 to 2010.[18] TIA was previously considered a benign condition compared to ischemic stroke.[10] However, TIAs have the same underlying mechanism as ischemic strokes, but due to rapid and spontaneous recanalization or sufficient collaterals that ensure tissue perfusion, the neurological deficits are reversed, and no permanent detectable brain injury occurs. Patients presenting with TIA carry a substantial risk of imminent ischemic stroke as up to 15% is reported to suffer a stroke within 90 days, with approximately half occurring within the first 48 hours.[10] Incidence rates of TIA range from 0.37 to 1.1 per 1000 annually, but precise estimates are difficult to determine because of varying definitions and criteria.[10] The true incidence of TIA is likely to be greater, as some TIAs may erroneously be attributed to other etiologies like migraine, anxiety, presyncope, and seizures, and many patients who experience neurological symptoms quickly passing by, and consistent with a TIA, do not feel a need to seek medical attention.[19]

In 2010, the economic costs of stroke in Europe were estimated to € 64 billion. The average costs of an incident stroke were € 21 000, and the costs of a prevalent stroke were € 5368.[20] The estimations were based on the combined costs of treatment, rehabilitation, disability, subsequent nursing and absence from work. The average life-time costs of an incident stroke in Norway in 2007 were estimated to 600 000 NOK with the highest costs during the first year, and the total yearly costs related to stroke-care were estimated to 7-8 billion NOK.[21] Lower age, more comorbidity, and increasing stroke severity and disability are the factors that have the highest impact on the costs of stroke.[22]

Ischemic stroke and TIA mechanisms

Ischemic stroke and TIA may be caused by thrombosis, embolism, or hypoperfusion. Thrombosis refers to obstruction of blood flow due to a localized occlusive process within an artery, reducing the blood flow distally, or giving rise to an embolus that occludes a more distant vessel. Embolism refers to obstruction of blood flow caused by a thrombus formed elsewhere within the vascular system, either in the heart, the aortic arch, the pre-cerebral or intracerebral arteries. Embolism may also occur as a paradoxical event by a thrombus from veins, passing by a right-to-left shunt to the arteries. Hypoperfusion refers to decreased blood flow or perfusion in a region of the brain caused by conditions disturbing cerebral perfusion, such as high-grade stenosis in pre-or intracerebral arteries or systemic hypoperfusion, concomitantly with insufficient collaterals.[23] This usually causes infarctions in the border zone vascular areas termed watershed infarction.

The underlying cause of the ischemic event influences both short-term and long-term prognosis and has important implications regarding secondary prevention. For this reason, several systems with different criteria have been developed for classification of ischemic stroke etiology. The most internationally used causative etiological classification in research to date is the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. The criteria are based on clinical features and result from brain imaging, duplex imaging of extracranial arteries, arteriography, cardiac tests and imaging and laboratory assessment for prothrombotic states.[24] The TOAST classification classifies ischemic stroke and TIA in five categories based on the most likely cause: large-artery atherosclerosis, cardioembolism, small vessel occlusion, other determined etiology, and undetermined etiology. Improved diagnostic tools and high percentages of undetermined etiology according to the TOAST classification have led to modifications such as the SSS-TOAST (Stop Stroke Study) and CCS (Causative Classification System), and development of other classification systems such as the ASCO (Atherosclerosis, Small-vessel disease, Cardiac source, Other cause) and CISS (Chinese Ischemic Stroke Subclassification).[25] The overall

agreement between the classification systems are moderate, making the comparability and interpretation across studies difficult.[26, 27]

Large-artery atherosclerosis (LAA). Atherosclerosis is a multifactorial, slowly progressing, systemic and chronic inflammatory disease that can develop in large and small arteries. Atherosclerosis may affect multiple organs and lead to cardiovascular disease, including cerebrovascular disease. Sites predisposing for development of atherosclerosis are branching arterial sites and vessel curvatures due to alterations in the blood flow, causing increased turbulence and decreased shear stress.[28] For the arteries supplying the brain, atherosclerosis mainly affects larger pre-cerebral and cerebral arteries that may result in artery-to-artery embolism, thrombosis, or hypoperfusion.[29] The TOAST classification requires either a >50% stenosis or occlusion of a major brain artery or branch cortical artery on vascular imaging for classifying a stroke as LAA, and does not take into account the importance of smaller unstable plaques.[24] The frequency of stroke due to LAA varies from 9% to 32% in different studies depending on the study population and classification used,[30-36] with the highest share in middle-aged stroke patients.[32, 37]

Cardioembolism (CE). Embolism from the heart to the brain can result from nearly all heart diseases due to stagnation of blood and formation of cardiac thrombosis, and from venous embolism crossing onto the arterial site in case of defects in the heart septum. The most frequent cause of CE with increasing age is atrial fibrillation. Individuals with AF have a 3-to 5-fold increased risk of stroke.[38] Other cardiac conditions associated with ischemic stroke and TIA are heart failure, myocardial infarction, prosthetic heart valves, endocarditis, patent foramen ovale, and rarer causes like myxoma, mitral calcification, and papillary fibroelastoma.[39] CE stroke represents 9% to 33% of all ischemic strokes and is frequent at all ages, but increases with age.[30-36]

Small vessel occlusion (SVO). Small vessel disease, also called microangiopathy, refers to structural changes of the small perforating cerebral arteries and arterioles termed lipohyalinosis, characterized by a thickened and stiff vessel wall with the

replacement of smooth muscle cells by foam cells and collagen, causing a narrowed vessel lumen and in some cases occlusion.[40] Imaging features of small vessel disease are small, deep-seated infarcts ≤20 mm primary in the white matter, basal ganglia, capsula interna, thalamus or brainstem called lacunar infarctions, deep-seated fluid-containing cavities ≤15 mm representing old infarctions called lacunes, primary intracerebral hemorrhages, white matter hyperintensities, microbleeds, visible perivascular spaces and brain atrophy.[40] SVO may also gradually cause cognitive and physical disability, leading to depression and dementia.[40] The frequency of ischemic stroke due to SVO varies from 7% to 25%,[30-36] and is more common in middle-aged and older stroke patients.[32, 37]

Stroke of other determined etiology (SOE). Ischemic stroke and TIA can be caused by spontaneous or traumatic arterial dissection, in which a tear in the intima of the arterial wall causes an intramural hematoma that may obstruct the arterial lumen or cause intraluminal thrombosis and distal embolization.[41] Other defined causes are hematologic abnormalities due to high blood cell counts or abnormal blood cells, deficiencies of natural anticoagulants, pro-thrombotic conditions in pregnancy, and malignancy.[42-44] Migraine is associated with ischemic stroke, especially in women with migraine with aura.[45] Non-atherosclerotic vasculopathies such as fibromuscular dysplasia and infectious or non-infectious vasculitis, and a number of hereditary metabolic disorders are other causes among SOE.[46] SOE is more common in stroke patients <50 years of age.[37] In the TOAST classification, these are all classified as SOE.[24]

Stroke of undetermined etiology (SUE). In some cases, the etiology of the stroke is not found, either despite adequate diagnostic evaluation (cryptogenic stroke), or because not all necessary investigations are performed. In others, there may be two or more potential causes of the stroke, and it cannot be determined which of them was causative.[24, 47] Stroke of undetermined etiology refers to all three cases, where the cause of the ischemic stroke or TIA cannot be determined with any degree of confidence and does not meet the criteria for an established subtype. [24]

Modifiable stroke risk factors

Risk factors of stroke can be stratified into non-modifiable and modifiable risk factors. Factors related to natural or hereditary processes such as age, sex, ethnicity, family history, and genetics have impact on stroke prevalence and ischemic stroke subtypes, but they cannot be modified.[32, 37, 48, 49] Modifiable risk factors relate to lifestyle choices and environment and are factors that can be prevented or modified by the use of medical treatment and lifestyle changes. More than 90% of all strokes and 90% of the stroke burden are attributable to modifiable risk factors.[50] These risk factors may potentiate each other if coexistent,[49] and are not exclusive to stroke, but also to other cardiovascular disease, such as coronary artery disease and peripheral artery disease, or to cancer. However, some modifiable risk factors may also have genetic components, such as known for some forms of hypertension, diabetes mellitus, and hypercholesterolemia.

Hypertension. Hypertension is the most important modifiable risk factor for ischemic and hemorrhagic stroke, and the risk increases with increasing blood pressure, even including the non-hypertensive range.[49] The prevalence of hypertension among Norwegian stroke patients was 57% in 2017.[51] Hypertension is also a major risk factor for other cardiovascular diseases, including coronary heart disease, heart failure, peripheral artery disease, and kidney failure.[52]

Diabetes mellitus. Diabetes mellitus is a major risk factor for cardiovascular diseases, especially in patients younger than 65 years of age.[49] It has been suggested that the presence of diabetes mellitus more often results in irreversible ischemic damage, more severe stroke, slower recovery, and higher mortality.[53, 54] The prevalence of diabetes mellitus in Norwegian stroke patients was 17% in 2017.[51]

Coronary and peripheral artery disease. Symptomatic and asymptomatic atherosclerosis in the coronary and peripheral arteries is a marker of systemic atherosclerosis, and a risk factor for extracranial artery disease and stroke.[55, 56] Stroke risk factors are shared with atherosclerotic disease in other territories, and the

presence of coronary or peripheral artery disease is associated with recurrent arterial events and a worse long-term outcome after stroke.[57]

Dyslipidemia. Dyslipidemia, especially high cholesterol, is a risk factor for cardiovascular disease.[49] The causal association with stroke is less clear and limited to specific stroke subtypes, particularly LAA and SVO.[32, 58] The prevalence of hypercholesterolemia in Norwegian stroke patients was 35% in 2017.[51]

Smoking. Cigarette smoking is the attributable cause in up to 25% of all strokes.[59] The relationship between cigarette smoking and stroke is dose-dependent, with increasing risk with the number of cigarettes smoked per day. Smoking is harmful to nearly every organ in the body and attributes to many diseases including cardiovascular disease, cancer, pneumonia, and chronic obstructive pulmonary disease.[60]

Other lifestyle factors. Both irregular and chronic heavy alcohol consumption increases the risk of ischemic stroke, as well as diseases of the liver, pancreas, gastrointestinal tract, the heart, cancer, and osteoporosis.[49, 61] Other lifestyle factors which may increase the risk of stroke include physical inactivity, obesity, diet, and illicit drug use that may lead to hypertension and diabetes mellitus.[49]

Inflammation. Results from several studies have demonstrated an associated between inflammatory conditions and ischemic stroke.[62, 63] Important features of this complex process is the anti-inflammatory response with activation of the coagulation.[64] Furthermore, chronic infections and inflammation can trigger and accelerate atherosclerosis.[62] Between 10 and 40% of ischemic stroke patients have had an acute infection during the week preceding stroke, most commonly in the respiratory tract.[63] Furthermore, some evidence point to a protective effect of influenza vaccination against stroke, although this is still debated.[65-67]

Treating stroke

Reduction of stroke incidence, disability, recurrence, and mortality involves five aspects; 1) primary prevention, 2) acute treatment with thrombolysis and thrombectomy, 3) hospitalization with clinical workup, treatment, and prevention of complications, 4) secondary prevention, and 5) rehabilitation including physiotherapy, occupational therapy, and speech and language therapy. As most recurrent strokes are caused by the same mechanism as the initial stroke, identification of the stroke mechanism is of utmost importance in secondary stroke prevention.[68] However, some patients may also have other underlying conditions that can lead to a subsequent stroke, and therefore, detection and treatment of comorbidity is important in order to reduce the risk of recurrent stroke. Secondary prevention has additional effects on reducing the development of other vascular diseases, cardiovascular mortality, and all-cause mortality.

Treating modifiable stroke risk factors impacts both primary and secondary prevention. Lifestyle modifications including smoking cessation, weight reduction in obese patients, limited alcohol consumption, salt restriction, adherence to a Mediterranean diet, and physical activity are important to reduce the risk of recurrent stroke, cardiovascular complications, and mortality.[69] These measures are also reasonable parts of antihypertensive and lipid-lowering therapy. All stroke patients with either known or newfound hypertension should be treated with antihypertensive medication.[69] Use of antihypertensive treatment and reduction in blood pressure reduces the risk of recurrent stroke, myocardial infarction, and cardiovascular death.[70] Lipid-lowering therapy should be provided for all patients with known hyperlipidemia, coronary artery disease or atherosclerosis in other territories. Lipid-lowering therapy reduces the risk of recurrent stroke even in the absence of cardiovascular comorbidity and hyperlipidemia for all stroke patients, but especially for those with IS or TIA assumed to be of atherosclerotic origin.[69, 71] Good and consistent blood glucose control reduces microvascular complications and macrovascular complications in patients with impaired glucose intolerance or diabetes mellitus.[72]

Patients with a stroke of atherosclerotic origins such as LAA or SVO should be treated with antiplatelet therapy.[73] A combination of acetylsalicylic acid and dipyridamole is often used if tolerated by the patient, as it is at least as effective as monotherapy for secondary stroke prevention.[74] Clopidogrel monotherapy is an alternative to aspirin or the combination of aspirin and dipyridamole.[69] Carotid surgery or endovascular stenting are recommended in patients with stenosis ≥70% of the proximal carotid artery and ipsilateral cerebral infarction, with a reduction in absolute risk of five-year stroke recurrence from 4.6 to 16%.[69, 75, 76] Carotid surgery in ischemic stroke or TIA patients with a moderate ipsilateral stenosis (50-69%) is recommended depending on patients specific factors such as age, sex, and comorbidity.[69, 76] Early surgical intervention between 48 hours and 14 days after a TIA or minor disabling stroke is recommended in selected patients due to a high risk of early recurrent stroke.[69, 77, 78] For patients with stroke of cardiac origin, anticoagulation is superior to platelet inhibitors, with a reduction in the annual stroke rate from 12% to 4%,[79] but the annual risk of major bleeding is slightly increased (1.3% versus 1% in patients treated with platelet inhibitors or placebo).[80] The duration and intensity of the treatment with anticoagulation depends on the underlying cardiac cause of the stroke.[69] Treatment of arterial dissection includes anticoagulation or antiplatelet therapy for at least three to six months, and endovascular treatment with stenting may be considered in patients with recurrent events despite medical therapy.[69]

Most strokes result from systemic diseases which may additionally affect other organs and the patient's general health. In addition to the secondary prevention of recurrent stroke and cardiovascular events, detection of swallowing problems, maintenance of adequate nutrition, cognitive and physical rehabilitation, and prevention and care of post-stroke complications are key factors in caring for a stroke patient. Admission of stroke patients to dedicated stroke units and centers improves stroke outcomes by limiting stroke morbidity, reducing the need for institutionalized care, improving quality of life after stroke, and reducing short-term and long-term mortality.[81-83]

Outcome and complications

The most used parameters for determining outcome after stroke are degree of dependency and death. Although ischemic stroke mortality has declined over the last decades, it remains a major cause of long-term institutionalization and one of the leading causes of death worldwide.[18] The risk of death is highest within the first 30 days after stroke onset.[84] In the Norwegian National Stroke Registry, the overall in-hospital mortality rate after stroke was 8.1% in 2017.[51] The most important factors affecting outcome after stroke are advancing age and stroke severity, including neurologic impairment and size and location of the infarction.[85-88] Comorbidities like coronary artery disease, heart failure, diabetes mellitus, cancer, and renal dysfunction also increase the risk of poor outcome.[86, 88, 89]

Stroke outcome is also highly related to complications. Between one-fourth and three-fourths of all stroke patients experience either neurological or medical complications.[90, 91] Neurological complications include brain edema, hemorrhagic transformation, recurrent stroke, neurological deterioration, seizures, epilepsy, and delirium, whereas medical complications include a wide range of complications of the heart, lungs, gastrointestinal tract, and genitouritrary system, and other conditions like venous thromboembolism, fractures, decubitus ulcers and psychological conditions. In general, medical complications are more frequent than neurological ones, but neurological complications occur earlier and usually within 48 to 72 hours after stroke onset, whereas medical complications usually develops within weeks after stroke onset.[2, 92, 93] However, both may occur up to several years after the initial stroke, and adversely affects the post-stroke outcome with increased physical and cognitive disability and higher short-term and long-term mortality.[2, 92-94] Post-stroke complications often lead to prolonged hospitalizations, delayed rehabilitation, hospital readmission, and increased costs.[92, 95, 96]

Readmission after ischemic stroke and TIA

Hospital readmission is defined as a new admission to the same or another hospital within a specified time interval after discharge. Readmissions may reflect different problems or a combination of problems and are often used as an outcome measure in addition to disability and death. Readmissions may result from poor quality of care during initial admission or afterward, caused by incomplete treatment, unresolved problems, poor care of underlying problems, inadequate communication and misunderstandings, and poor coordination of services such as discharge planning or access to health care. For this reason, readmissions are frequently used as a quality-indicator for health care services. Readmissions may also reflect an old and chronically ill population with substantial disability and morbidity and a high risk of deterioration of chronic conditions and a higher occurrence of complications. Individuals with chronic diseases, usually increasing with increasing age, have different clinical needs than persons without chronic diseases and a more rapid decline in health status and a greater chance of disability and repeated hospitalizations.[97]

Hospital readmissions impose a great burden on the health care system that demands a significant share of the available health care resources concerning personnel, hospital beds, and health care costs. A study from the US estimated that readmissions generated approximately one-fifth of all Medicare costs between 2003 and 2004.[98] Readmission rates have been steadily increasing, and in 2016, early readmissions accounted for about 9% of all day-care and bed days in Norwegian hospitals.[99] Stroke patients are one of five patients groups which show the highest numbers of readmissions in Norway.[4] Studies have shown that the healthcare payments related to stroke patients increase with each readmission, and a considerable share of the first-year healthcare payments of stroke patients are spent on readmissions.[3, 100] There are no precise estimates of the costs of readmissions after stroke in Norway, but a study from Scotland estimated the mean costs per readmission after an ischemic stroke to £4,487 in 2004.[101]

New acute illnesses in addition to the stroke cause more morbidity and interfere with post-stroke recovery, which may further lead to a reduced cognitive and physical function and higher mortality. The likelihood for surviving for one year after stroke declines with increasing numbers of early readmissions, from 83% in patients with no readmission to 67% in patients with one readmission, to 55% in patients with 2 or more readmissions.[3] The early period following discharge represents an especially vulnerable period for readmission, as readmission within the first 90 days represents more than half of all readmission happening within one year after discharge.[102-105] Within five years, less than 15% of all stroke patients are alive and have never been readmitted, and after ten years, the number of patients alive and never readmitted declines to 6.6%.[105, 106]

Links between stroke and other diseases

Infections. Infections complicate up to 30% of all strokes in the acute phase and have a negative impact on the post-stroke outcome with higher rates of dependency and mortality.[107] Three interacting mechanisms likely contributes to development of post-stroke infections; (1) neurological deficits such as dysphagia, impaired cough reflex, hypoventilation, bladder problems, and reduced mobility, (2) procedures like intubation, nasogastric tube feeding, and urinary catheterization, and (3), stroke-induced immunosuppression, characterized by autonomic dysregulation causing alterations in immune cell function and number. The suppression of the immune system minimizes excessive inflammation in the injured brain but consequently increases the susceptibility for infections.[108] A fourth possible cause is infections before the stroke which manifests or worsens after stroke onset. Infections have been shown to precede and trigger stroke in many studies, and infection, especially in the week before stroke onset, is an independent risk factor for ischemic stroke.[63] As swallowing dysfunction and bladder problems frequently follow stroke, the most frequent post-stroke infections are pneumonia and urinary tract infection (UTI).

Stroke patients who develop pneumonia have a significantly poorer long-term outcome and higher mortality than patients without pneumonia.[109] Stroke-associated pneumonia is usually caused by aspiration related to swallowing impairment or a decreased level of consciousness.[2, 90] Contrary to pneumonia, most UTIs after stroke are uncomplicated and does not affect stroke outcome when other factors like stroke severity and premorbid status are taken into account.[90, 110]

Recurrent stroke. Ischemic stroke and TIA patients are at considerable risk of suffering further strokes compared to the general population, and recurrent strokes are more likely to be disabling or deadly.[111-113] The risk of recurrent stroke is especially high during the first weeks after the onset of stroke symptoms and declines over time.[114] The combined annual risk of recurrent stroke after IS or TIA was found to be 4.3% in a meta-analysis of 34 studies.[114] Treatment adherence and occurrence of cardiovascular risk factors have profound impact on the risk of recurrent stroke. Major risk factors for recurrent stroke include increasing age, hypertension, atrial fibrillation, carotid stenosis, cardiac disease, smoking, and diabetes mellitus.[91, 115]

Coronary artery disease. Stroke and coronary artery disease share many risk factors and pathogenic processes. Accumulating evidence suggests that even in the absence of known risk factors and cardiac disease, suffering a stroke is a risk factor for having underlying coronary artery disease.[116] The annual risk of myocardial infarction in a recent meta-analysis was 1.67%, and the risk increased more than a 3-fold in patients with a history of coronary artery disease compared to patients with no history of coronary artery disease.[114] Risk factors for myocardial infarction after stroke include male sex, hypertension, and a history of coronary artery disease or peripheral artery disease.[114] Atherosclerosis is the primary cause of coronary artery disease, and patients with LAA as cause of the stroke have generally a higher occurrence rate of coronary artery disease.[117, 118]

Venous thromboembolism. Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism, is a major concern after stroke.[90] Severe stroke, immobilization, limb paralysis, high age, dehydration, and acute medical

conditions predispose patients to DVT development, which may result in persistent limb pain, swelling and venous ulceration (post-thrombotic syndrome) or pulmonary embolism.[90, 119] Clinically overt pulmonary embolism occurs in 1% during the first two weeks after stroke onset.[120] The risk of VTE after stroke is highly increased during the first three months after stroke and decreases rapidly after that.[90] In the Tromsø study, the risk of VTE was considerably increased during the first three months after an ischemic stroke, with a 20-fold increased risk the first 30 days and an 11-fold increased risk in the second and third month. After three months, the risk was almost the same as for the general population.[119]

Cardiac disease. Shared risk factors between stroke and cardiac conditions and underlying diseases of the heart causing the stroke, make cardiac diseases common in stroke patients. The brain damage caused by the stroke can also induce autonomic dysfunction, which together with physiological stress makes cardiac dysfunction a frequent accompaniment of stroke in the acute phase.[121] It usually manifests as a mild and reversible dysfunction which resolves in a few weeks, but it can also cause life-threatening conditions like myocardial infarction, ventricular arrhythmias, heart failure, and cardiac arrest, and lead to long-term cardiac damage.[121] Arrhythmias frequently follow stroke or can be the cause of stroke, as in the case of atrial fibrillation. The occurrence of new arrhythmias are particularly high the first few days after stroke, and up to 67% of all ischemic stroke patients have ischemic or arrhythmic abnormalities on ECG.[90, 121] Heart failure is common in stroke patients, both as a concurrent condition because of an aging population with structural or functional damage to the heart, or as a complication of stroke due to new-onset myocardial infarction, acute hypertension, or iatrogenic complications such as changes in medications or fluid overload.[90, 121] Concurrent stroke and heart failure have an adverse effect on each other, with stroke increasing the severity and duration of heart failure, and heart failure leading to increased stroke severity and post-stroke complications.[122]

Neurological deterioration. Neurological deterioration after stroke is a frequent and feared complication in acute stroke patients that usually occurs within the first week

after onset.[91, 123] Signs include progression of focal neurological symptoms or a decrease in the level of consciousness, and can be caused by brain edema, hemorrhagic transformation, a progression of brain ischemia, propagation of thrombus, metabolic disturbances, hypotension, seizures, delirium or recurrent stroke.[91] Neurological deterioration is less common in the sub-acute and chronic phase after stroke but may occur in relation to seizures, recurrent stroke, metabolic disturbances, or infections.[123]

Seizures and epilepsy. Stroke is the most common cause of acute symptomatic seizures and epilepsy in adults over 34 years of age.[124] Post-stroke seizures are divided into early seizures occurring within one to two weeks, and late seizures manifesting later than two weeks.[91] Early seizures may be related to cellular biochemical dysfunction leading to electrically irritable tissue and occur in 2% to 23% of all stroke patients.[125] Late seizures are thought to be caused by permanent lesions and occur in 3% to 67%.[125] More than 50% of patients with late-onset seizures have recurrent seizures, and they have a higher likelihood of developing chronic epilepsy than patients with early-onset seizures, but the risk of developing epilepsy is still higher after an early-onset seizure compared to stroke patients without early-onset seizures.[91, 125] Cortical lesions and increasing stroke severity are the most consistent risk factors for post-stroke seizures and epilepsy.[125-128] Young stroke patients also have a higher risk of post-stroke epilepsy, but this could be caused by survival rather than increased susceptibility to epileptogenesis.[126, 128]

Fractures. The risk of fractures increases considerably after a stroke.[129, 130] Falls may occur due to balance difficulties, neglect, sensory loss, visual problems, cognitive or motor impairment, seizures, or use of sedative medication.[90, 131] The incidence of post-stroke falls varies considerably among studies, ranging from 23% to 34% at 3 to 4 months, and 40% to 70% within one year.[132] Bone-density changes with increased bone resorption secondary to bed rest, immobility and paretic limbs in combination with age-associated osteoporosis in older stroke patients increase the risk of fractures.[133] Compared to healthy individuals of comparable age, stroke patients with paretic lower or upper limbs have up to a 10-fold and 20-fold higher bone resorption,

respectively.[134] Most fractures occur on the paretic side secondary to falls, and almost half of all fractures involves the hip joint.[135, 136] Compared to a non-stroke population, the risk of fractures is increased up to a 7-fold during the first year after stroke.[129]

Gastrointestinal bleeding. Gastrointestinal (GI) bleeding is the most common source of major extracranial bleeding after stroke. Approximately 1.5% to 5% of all strokes are complicated by GI bleeding, most often occurring in the upper GI tract.[2, 137, 138] GI bleeding is associated with recurrent stroke, myocardial infarction, and VTE and has a significant impact on post-stroke dependency and mortality.[90, 138]

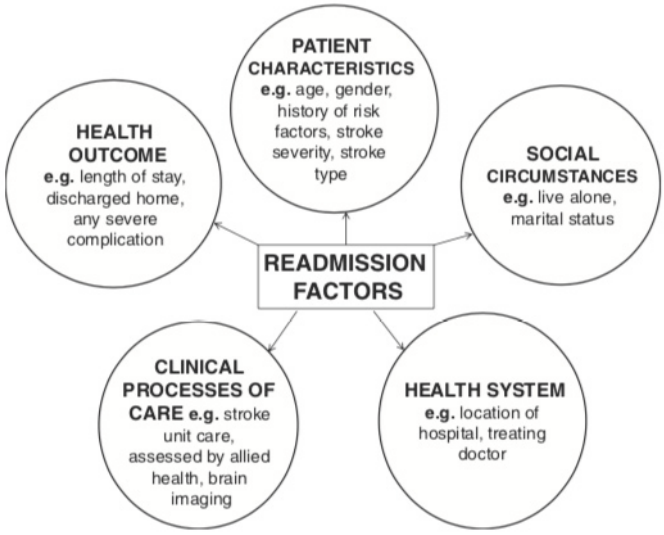
Risk factors for readmission after ischemic stroke and TIA

Hospital readmissions have been receiving increased attention as it may be a correctable source of excessive spending and poor quality of care. Information on reasons why readmissions occur can help prevent avoidable readmission by assisting clinicians and health care institutions in identifying high-risk patients and further initiate interventions to prevent readmission. Therefore, readmission risk prediction models have gained increasing attention. Clinically relevant stratification of readmission risk could contribute with information that would trigger interventions during hospitalization and in the immediate period after discharge. A systematic review from 2011 including studies of readmission after various diseases identified 26 unique models for predicting the risk of readmission.[139] Most of the studies included variables of medical comorbidity and prior hospitalizations, but few consider parameters related to disease severity, functional outcome and social determinants of health.[139]

Since stroke is a frequent cause of hospital readmissions, and readmission after stroke results in adverse outcomes for patients and generates high health care costs, many studies have tried to identify factors that influence the readmission rate among stroke patients. There are different aspects of reasons which might lead to readmission that

have to be considered in the identification of factors related to readmission after stroke (Figure 1). Patient characteristics, such as age, cardiovascular risk factors, and comorbidity, may generate a higher risk of readmission by the development of a new disease or worsening of co-existing disorders. Stroke specific measures, such as the degree of neurological deficits, stroke severity and functional disability may have impact on the readmission risk, as these measures are related to post-stroke complications and outcome. Measures on clinical process of care, health system and health outcomes, such as stroke unit care, duration of the index admission, occurrence and treatment of complications during index admission, and discharge planning might provide information on the quality of the provided care. It might be an especially valuable approach to identify potentially preventable readmissions. A final aspect is social circumstances and socioeconomic status, which can influence all of the other mentioned aspects.

Figure 1. Categories of factors that may be associated with readmission after ischemic stroke and TIA.



Adapted from Kilkenny MF et al., Stroke 2013.[140] With permission of the publisher

A systematic review from 2010 identified 16 studies examining the risk of readmission after stroke.[141] Several risk factors were identified, but there was little consistency between the included studies and a considerable heterogeneity in the selection of covariates that could be related to readmission. Furthermore, the review did not identify any studies that provided a risk-standardized model for prediction of readmission risk after stroke.

As ischemic stroke and TIA are heterogeneous disorders caused by various diseases, many of the aspects that should be considered when investigating factors associated with readmission after stroke can be influenced by the stroke subtypes. Although studies show some varying results in the distribution and frequency of the different cardiovascular risk factors, stroke patients with LAA or SVO have the highest occurrence of hypertension, hyperlipidemia, diabetes mellitus, and smoking, which is likely related to the pathogenesis of these diseases.[32, 35, 40, 142, 143] Stroke patients with LAA also have the highest prevalence of coronary artery disease, peripheral artery disease, and TIA.[32, 33] Stroke patients with CE are the oldest among the stroke subtypes, and stroke patients with SOE are usually the youngest.[32, 142] The most severe strokes and subsequently high functional disability is found in stroke patients with CE, whereas SVO is associated with milder deficits.[144]

The differences in age, cardiovascular risk factor profile, comorbidity, and stroke severity between the stroke subtypes results in different risks of new cardiovascular events, cardiovascular mortality and overall mortality.[32, 144] Specific associations of risk factors for readmission could be diluted and underestimated in analysis combining all subtypes into one stroke category. Only a minority of studies about readmission after stroke have included information on ischemic stroke subtypes. Characterization of incidence and causes of readmission after stroke according to stroke subtype might provide a more detailed understanding of why stroke patients are readmitted and contribute to more effective secondary prevention of not only recurrent stroke and vascular events, but also other diseases.

Aims of the thesis

1. To assess the rates and incidence of short-term and long-term unplanned hospital readmission after ischemic stroke or TIA.

2. To assess the most frequent causes of short-term and long-term unplanned hospital readmission after ischemic stroke or TIA.

3. To assess factors associated with unplanned hospital readmission within different periods after ischemic stroke or TIA.

4. To assess similarities and differences in risk factors for patients readmitted within different periods after ischemic stroke.

5. To assess the impact of ischemic stroke subtype on the incidence and causes of hospital readmission to elucidate the underlying causes of readmission.

6. To assess the impact of thirty-day readmission after ischemic stroke or TIA on one-year mortality.

Material and methods

Bergen NORSTROKE registry

Data for all papers in the thesis have been obtained from the NORSTROKE registry, and from the medical journals of all included patients after discharge from the stroke unit at Haukeland University Hospital.

NORSTROKE has since 2006 prospectively registered all patients >18 years of age admitted with IS, intracerebral hemorrhage or TIA to the stroke unit at the Department of Neurology, Haukeland University Hospital. The stroke unit serves a well-defined geographical area of approximately 275,000 inhabitants, in addition to stroke patients <60 years of age from neighboring regions and all patients eligible for endovascular stroke treatment. The study has been approved by the Western Regional Ethics Committee and written informed consent is obtained from all patients or their legally authorized representatives.

All patients with suspected stroke were admitted to the hospital either directly or after examination in primary health care. Upon admission, patients were examined by a residence in neurology and scored by the National Institute of Health Stroke Scale (NIHSS) score. Urgent computed tomography (CT) was performed in all patients to assess early ischemic changes, hemorrhages, or other apparent causes of the symptoms. If the patients presented <6 hours after onset of symptoms, CT angiography was performed to assess possible occlusions available for endovascular treatment, unless contraindicated.

Unless contraindicated, all patients routinely underwent magnetic resonance imaging (MRI) and magnetic resonance angiography using 1.5 or 3 Tesla Siemens magneton (Symphony) on the day after admission. Not all patients with suspected TIA underwent MRI during the first years of the NORSTROKE Study due to a limited MRI capacity. A neuroradiologist and a stroke neurologist (HN) reviewed all MRI scans. Examination of the extracranial arteries was regularly performed by Duplex ultrasound within one day of admission by a resident or attending neurologist in the

Stroke Unit. Electrocardiography (ECG) was obtained in all patients, and patients with suspected cardioembolic etiology underwent echocardiography and Holter monitoring. All patients were mobilized early and referred to a professional rehabilitation team as appropriate.

NORSTROKE is conducted by a standardized form which is prospectively filled out during treatment and follow-up during stroke admission. NORSTROKE includes data on the patient's age, sex and time of symptom and admission, prior medical history and cardiovascular risk factors, clinical findings and vital parameters, results from examinations including radiological, neurosonological, cardiological and laboratory findings, treatment during admission, complications, medications prior to index admission and at discharge, short-term outcome, and discharge date and discharge destination.

Registered prior medical disease and stroke risk factors included hypertension (considered present if diagnosed by a physician before stroke onset), diabetes mellitus (considered present if glucose lowering diet or medication had been initiated before admission or if revealed by a HbA1c > 6.4% during hospital admission), and atrial fibrillation (considered present if confirmed by ECG at any time prior to admission or during hospital admission). Registration of prior stroke or TIA, myocardial infarction, angina pectoris, and peripheral artery disease were based on information from the patient, partner or relatives of the patient, or abstracted from the medical journal. Smoking habits were categorized as current smoker (at least one cigarette per day), previous smoker (cessation of smoking at least one year before stroke onset) and never smoker. A variable representing the total number of cardiovascular risk factors (0, 1, 2, ≥3) was made and defined as risk factor burden. Risk factor burden included hypertension, diabetes mellitus, smoking, angina pectoris, prior myocardial infarction, and peripheral artery disease. The risk factor burden has previously been associated with an increased risk of recurrent ischemic stroke.[145]

Stroke severity was determined by the NIHSS score. The score is a 15-item impairment scale ranging from 0 to 42, where a score of 0 is no neurological

impairment, and 42 is the most severe impairment. The NIHSS score is reliable and valid and the standard stroke impairment scale used in both clinical care and most clinical trials.[146] However, the score does not capture all stroke-related deficits, such as fine motor skills, tempo, and symptoms from areas supplied by the vertebrobasilar circulation.[147] The NIHSS score was assessed immediately on admission, after one hour and subsequently for standardized intervals by a stroke nurse in the stroke unit for evaluating improvement, stability or progression. Stroke in progression was defined as a worsening of 4 or more points from the admission NIHSS score. Patients were finally scored by the NIHSS score on day 7 or at discharge if earlier.

Short-term outcome was determined by the modified Rankin Scale (mRS) score and Barthel Index (BI) score day 7 or on the day of discharge if earlier. The mRS score measures function, and an mRS score 0-2 is generally regarded as favorable functional outcome while mRS 3-5 is regarded as unfavorable and poor outcome because of dependency, and 6 represents death (Appendix).[146] The BI measures ten basic aspects of self-care and physical dependency. Scores lower than 100 indicate an increased disability, a BI >60 corresponds to assisted independence, and a BI <40 corresponds to severe dependency.[148]

Based on findings from clinical examination and radiological, neurosonological, cardiological and laboratory assessments, ischemic stroke and TIA etiology was categorized by the TOAST classification as large artery atherosclerosis (LAA, localized or artery-to-artery embolism), cardioembolism (CE, medium or high risk), small vessel occlusion (SVO), stroke of other determined etiology (SOE, arterial dissection, hematological abnormalities, miscellaneous causes), and stroke of undetermined etiology (SUE, cryptogenic stroke, incomplete evaluation or competing etiologies) (Appendix). The etiology was determined by stroke neurologist Professor Halvor Naess.

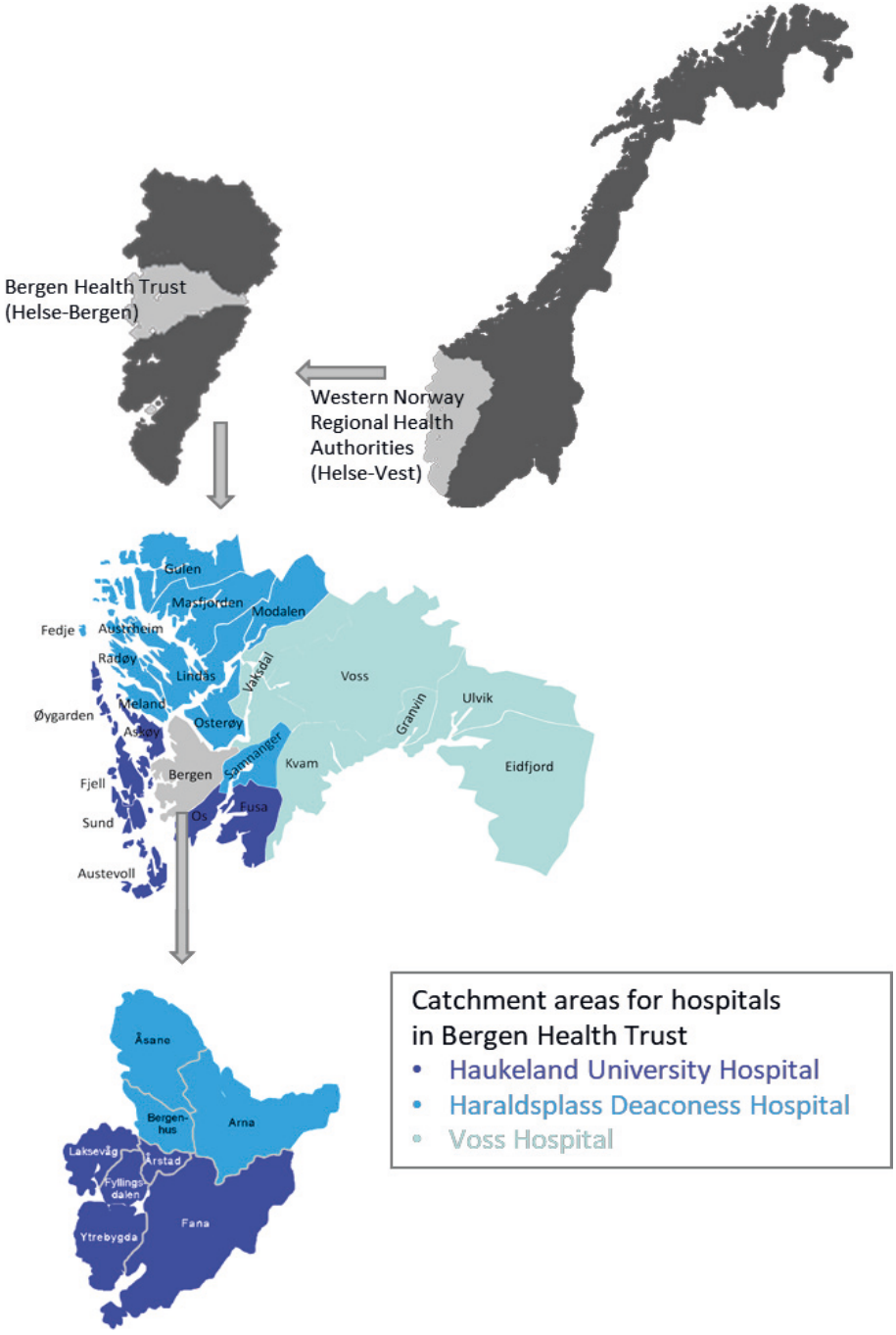
Readmission subtraction

Patients admitted between July 2007 and December 2013 to the Stroke Unit at Haukeland University Hospital were followed by review of electronic medical records. The electronic medical review included medical records from all ten hospitals in the region of the Western Norway Regional Health Authorities (Haukeland University Hospital, Haraldsplass Deaconess Hospital, Voss Hospital, Lærdal hospital, Nordfjord Hospital, Førde Central Hospital, Stord Hospital, Odda Hospital, Haugesund Hospital, and Stavanger University Hospital). The region is one of four regional health authorities in Norway, and includes approximately 1.1 million inhabitants in the counties of Rogaland, Hordaland and Sogn og Fjordane (Figure 2). Data on mortality after discharge was also extracted from the medical records, which is automatically and continuously updated from the Norwegian National Registry (Folkeregisteret).

Data collected for each readmission included the date of readmission, departments, primary diagnosis, secondary diagnoses, blood pressure, working status, current smoking, alcohol abuse, discharge date, and discharge destination. Medical treatment at first and last readmission and were registered, as well as the date of death. All readmissions were registered, but only unplanned (emergency) readmissions were included in the studies. Time from discharge to the first unplanned readmission represented time to readmission.

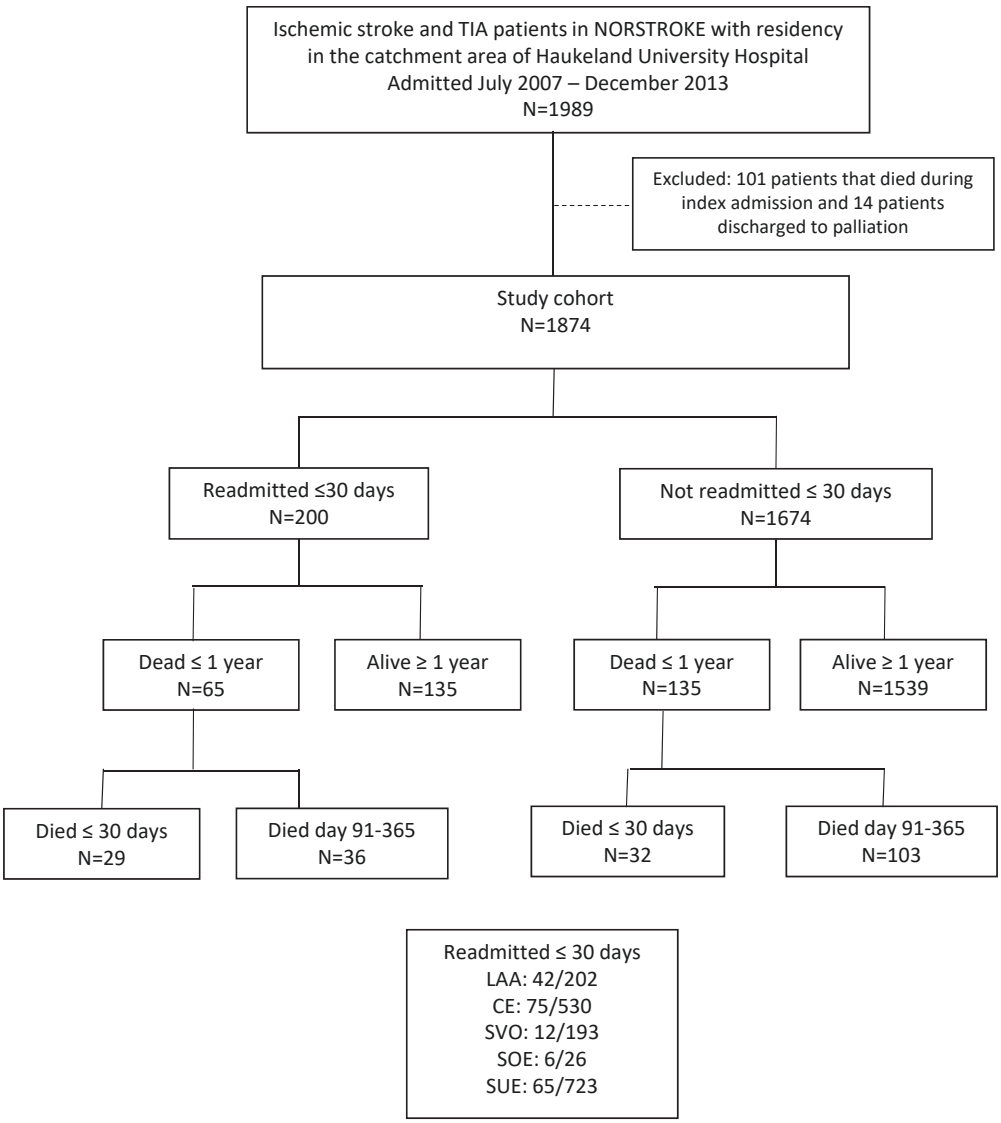
Only patients with residency in the catchment area of Haukeland University Hospital (Figure 2) at time of the index admission were registered and included in the papers of the thesis. Patients who died or moved outside the region of the Western Norway Regional Health Authorities during follow-up before any readmission had occurred were censored at the time of disenrollment.

Figure 2. The catchment area (local hospital) for Haukeland University Hospital

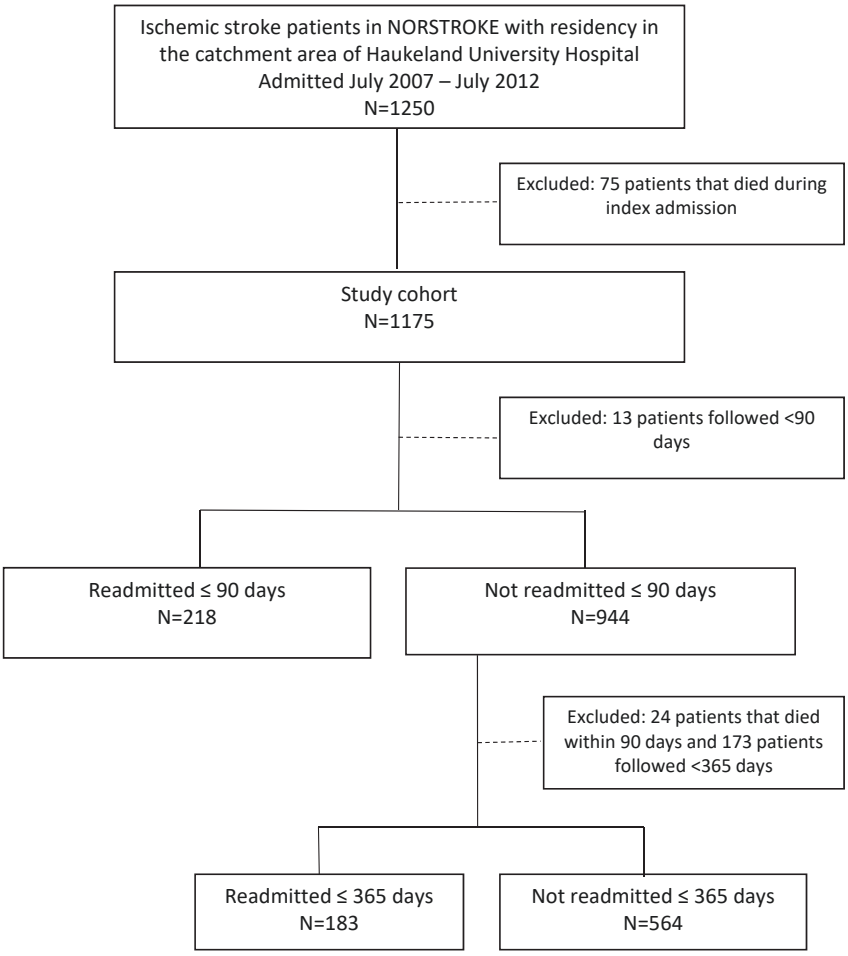


Study populations

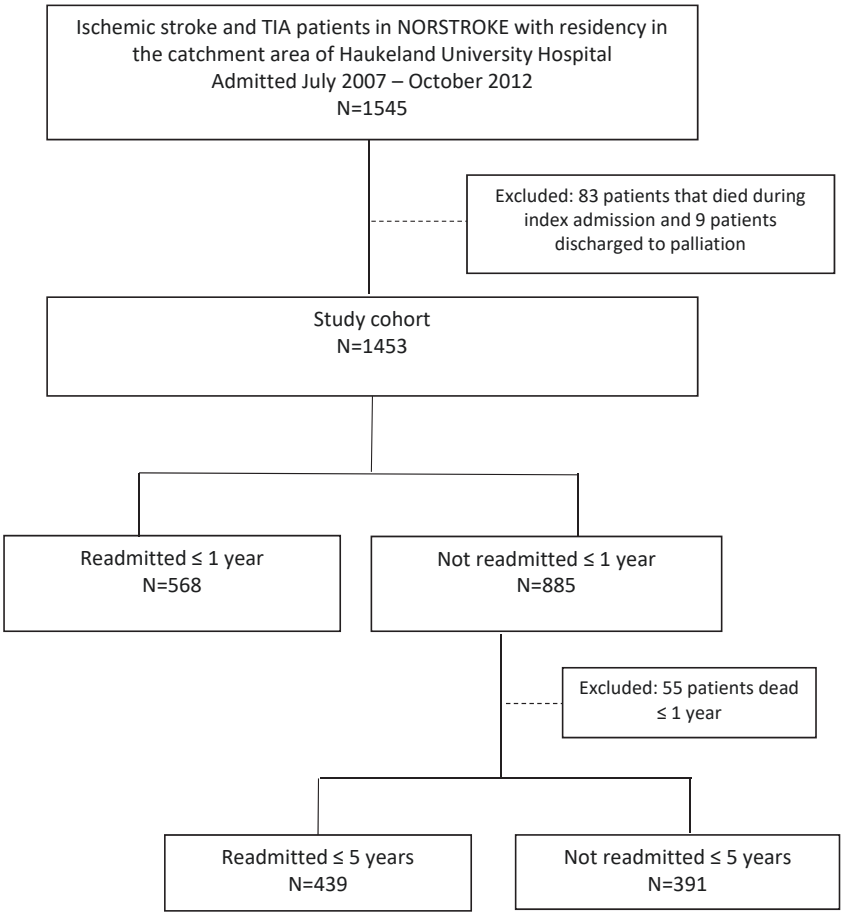
Paper I studied rates, causes and risk factors for readmission within 30 days after discharge in ischemic stroke and TIA patients. Patients admitted between July 2007 and December 2013 were included in the study, and the final study cohort included 1874 ischemic stroke and TIA patients. The study also examines the rates, causes, and risk of 30-day readmission for each stroke subtype, and the impact of 30-day readmission on one-year mortality in patients that were alive 30 days after discharge.



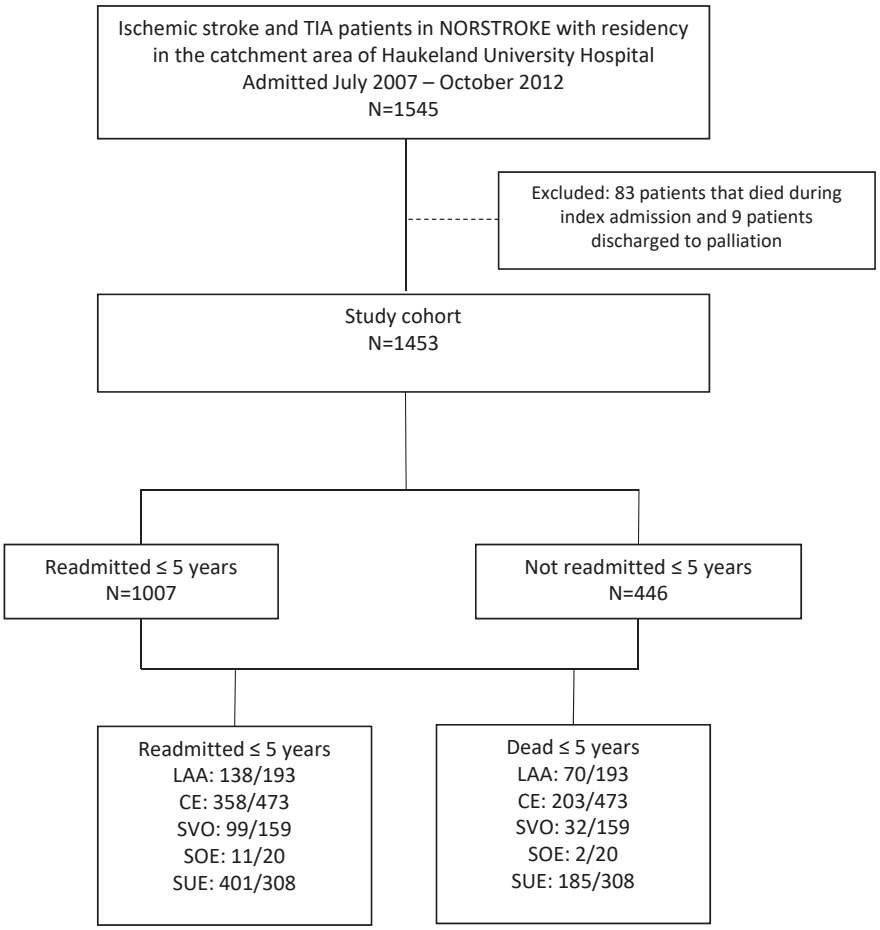
Paper II studied readmission within one year after discharge in patients admitted with ischemic stroke from July 2007 to July 2012. Of 1250 patients, 1175 survived the index admission and were included in the study. Due to administrative causes, only readmissions to Haukeland were included in this study. Readmitted patients were divided into two groups: those who were readmitted within 90 days after discharge (defined as early readmission), and those who experienced the first readmission from day 91 to 365 after discharge (defined as late readmission). Patients that could not be followed for the respective time intervals were excluded. For the analyses of late readmission, patients that were readmitted or dead within 90 days were excluded.



Paper III studied readmission within five years in the 1453 ischemic stroke and TIA patients that were discharged alive and could be followed for five years after discharge from the stroke unit. Readmitted patients were divided into two groups: those who were readmitted within one year after discharge, and those who experienced the first readmission between years 2-5 after discharge. For the analyses on readmission between years 2-5, patients that were readmitted or dead within one year were excluded.



Paper IV studied five-year readmission and mortality by ischemic stroke subtype. All patients with ischemic stroke or TIA that could be followed for five years after discharge from the index admission were included. After exclusion of 92 patients that died during the index admission or were discharged to palliative care, the final study cohort consisted of 1453 patients. All unplanned readmissions were included, and the incidences of all-cause and cause-specific readmission were calculated for each stroke subtype.



Statistics

The chi-square test was used for the univariate analyses of categorical variables. Student's *t*-test and one-way ANOVA were used for the univariate analyses of normally distributed continuous variables, whereas Wilcoxon rank-sum test and Kruskal-Wallis H-test were used for skewed continuous variables.

Kaplan Meier estimates were used to determine incidences of all-cause and cause-specific readmissions and mortality, and the log-rank test was applied for comparison of incidence estimates between the stroke subtypes. Kaplan-Meier failure curves were made to demonstrate the incidence of all-cause and cause-specific readmission and mortality over time. To evaluate for possible bias caused by the competing risk of mortality, we compared the Kaplan-Meier incidence estimates of all-cause and cause-specific five-year readmissions to age-adjusted cumulative incidence estimates from survival models that accounted death as a competing risk (Fine-Gray model).[149]

Multivariate analyses were performed using logistic regression and Cox regression by stepwise backward elimination starting with all statistically significant variables ($p<0.05$) from the univariate analyses. Age, sex, and mRS score have been forced into all regression analyses to adjust for potential confounding. Length of stay was additionally forced into the regression analysis on 30-day readmission, 90-day readmission, and 91-365 day readmission, and the risk factor burden and premorbid care-status were forced into the analyses on the risk of readmission for stroke subtypes.

Summary of papers

Paper I: 30-day hospital readmission

Of the 1874 patients with ischemic stroke or TIA that were discharged alive, 200 (10.7%) were readmitted within 30 days. There were significant differences in 30-day readmission among the stroke subtypes (LAA: 17.2%, CE: 12.4%, SVO: 5.9%, SOE: 18.8%, SUE: 8.3%). The overall most frequent causes of readmissions were a stroke-related event, infection, recurrent stroke/ TIA, and cardiac disease, but the rates varied significantly among the stroke subtypes. Factors that significantly increased the risk of 30-day readmission were increasing age (HR=1.02, 95% CI=1.01-1.03), peripheral arterial disease (HR=1.58, 1.01-2.47), enteral feeding (HR=1.86, 1.11-3.11) and LAA subtype (HR=1.74, 1.20-2.51). After adjusting for age, sex, functional outcome, length of stay and the risk factor burden, patients with LAA or SOE subtype had significantly higher risks of readmission for any cause (HR=1.76, 1.22-2.53 and HR=2.81, 1.11-7.10, respectively), recurrent stroke or TIA (HR = 3.31, 1.55-7.07 and HR=6.00, 1.26-28.57, respectively) and stroke-related events (HR=2.98, 1.55-5.74 and HR=4.27, 1.19-15.35). Thirty-day readmission increased the risk of death within one year (HR=2.57, 1.75-3.78).

Paper II: Hospital readmission within 90 days versus day 91-365

Of the 1175 ischemic stroke patients discharged alive, 18.8% were readmitted within 90 days, and 24.5% were readmitted for the first time between day 91 and 365 after discharge. Of the 943 patients that could be followed for one year, a total of 355 patients (37.7%) were readmitted at least once within one year. The most frequent causes of readmission during both periods were infections, recurrent stroke, cardiac disease, and stroke-related event. Early readmission was associated with increasing age (OR=1.02, 95% CI = 1.00-1.03), poorer functional outcome (OR=1.21, 1.09-1.35), LAA subtype (OR=1.85, 1.17-2.92), atrial fibrillation (OR=1.54, 1.08-2.19) and increasing risk factor burden (OR=1.28, 1.08-1.51). Late readmission was associated with increasing age

(OR=1.02, 1.00-1.03) and prior myocardial infarction (OR=1.89, 1.18-3.04), whereas SVO subtype had a lower risk of late readmission (OR=0.56, 0.31-0.98). Early readmitted patients had a shorter length of stay during the index admission, poorer physical function and higher frequencies of LAA subtype, atrial fibrillation, and complications with infection during the index admission compared to patients readmitted late. More patients were readmitted with recurrent ischemic stroke or myocardial infarction within the first 90 days compared to the following 90 days (n=34 versus n=12, P=0.02). Pneumonia during the index admission significantly increased the risk of readmission for pneumonia within 90 days and from day 91-365, and urinary tract infection or urinary retention significantly increased the risk of readmission due to urinary tract infection within 90 days.

Paper III: Hospital readmission within one year versus the second and fifth year

The study included 1453 patients with ischemic stroke or TIA, of whom 568 (39.1%) were readmitted within one year. Of the 830 patients that were alive and without readmission one year after discharge, 439 (52.9%) were readmitted within five years. The most frequent cause of readmission during the first year was infections, followed by recurrent stroke and stroke-related event, whereas cardiac disease and infection were the most frequent cause of the first readmission for patients readmitted from the second through fifth year. Common independent risk factors of readmission within one year and from the second through fifth year were increasing age (HR=1.02, 95% CI = 1.01-1.03, and HR=1.03, 1.02-1.04, respectively), poorer functional outcome (HR=1.15, 1.09-1.22, and HR=1.09, 1.02-1.16, respectively), coronary artery disease (HR=1.29, 1.07-1.57, and HR=1.50, 1.20-1.89, respectively) and hypertension (HR=1.26, 1.05-1.50, and HR=1.38, 1.13-1.68, respectively). Peripheral artery disease was independently associated with readmission within the first year (HR=1.42, 1.06-1.89), and atrial fibrillation was associated with readmission from the second through the fifth year (HR=1.25, 1.01-1.55). Patients with SVO subtype had a significantly lower risk of readmission during the first year (HR=0.67, 0.49-0.91). Patients readmitted during the first year after discharge were older, had more severe

strokes, a poorer functional outcome, and a higher occurrence of complications during the index admission than patients readmitted from the second through the fifth year. Cardiovascular comorbidity and prescribed medication at discharge or at the time of readmission did not differ between the two groups of readmitted patients.

Paper IV: Five-year hospital readmission and mortality by stroke subtype

The five-year incidence of all-cause readmission after ischemic stroke or TIA was 72.6% (74% LAA, 81% CE, 65% SVO, 55% SOE, and 68% SUE). Stroke patients with CE or SVO had the highest admission and discharge NIHSS score, respectively, and the poorest short-term functional outcome. Stroke patients with LAA had the highest risk factor burden, and the highest occurrence of peripheral artery disease, hypertension, and smoking. The most frequent causes of readmission were infections (30%), cardiac disease (20%), stroke-related event (15%), recurrent stroke (14%), and fracture (12%). Table 2 demonstrates the cumulative incidence of all-cause and cause specific readmissions up to five years after discharge.

Table 2. Cumulative incidence of all-cause and cause-specific readmission up to five years after discharge from ischemic stroke or TIA hospitalization in the NORSTROKE population (N=1453).

	30 days	90 days	180 days	1 year	2 years	3 years	4 years	5 years
Total readmission	9.9	18.9	28.2	39.9	53.2	61.3	68.3	72.6
Recurrent stroke	1.7	2.8	3.8	5.7	8.1	9.8	12.1	13.8
Stroke-related event	2.2	3.5	4.7	6.6	10.0	11.9	13.8	14.9
Seizures	0.4	0.8	1.2	1.9	2.7	3.2	3.7	4.3
Cardiac disease	1.3	2.9	4.0	6.2	10.4	13.8	17.4	20.8
Infection	1.7	3.6	6.5	10.3	15.8	20.5	25.5	29.7
Fracture	0.4	1.1	1.4	3.5	5.4	7.7	10.4	12.3
GI hemorrhage	0.1	0.8	1.2	1.6	2.4	3.1	3.6	4.4
VTE	0.1	0.2	0.4	0.5	0.9	1.2	1.4	1.6
Other disease	2.7	6.6	11.0	17.7	27.4	33.7	40.7	46.5

The incidence of readmission due to infection, cardiac disease, and fractures varied significantly among the stroke subtypes. There was no difference in the incidence of

recurrent stroke or stroke-related events among the stroke subtypes. After adjusting for age, sex, mRS score, premorbid care-status, and the risk factor burden, SVO subtype had a 21% lower risk of all-cause readmission (HR=0.79, 0.64-0.98), and CE subtype had a 25% higher risk of all-cause readmission (HR=1.25, 1.09-1.43). CE subtype also had a 75% higher risk of readmission due to cardiac disease (HR=1.75, 1.35-2.25), whereas SUE was associated with a 23% lower risk of readmission due to cardiac disease (HR=0.77, 0.59-0.99).

After five years, 404 (40.1%) of the readmitted patients were dead compared to 88 (19.7%) of patients that had not been readmitted ($p<0.001$). The five-year mortality varied significantly among stroke subtypes, with the highest mortality observed in patients with CE. After adjusting for age, sex, mRS score, premorbid care-status, and the risk factor burden, CE subtype had a 34% higher risk of death within five years (HR=1.34, 1.12-1.61), and SVO had a 48% lower risk of death (HR=0.52, 0.36-0.74).

Discussion

Prevalence and causes of readmission after ischemic stroke and TIA

The focus on hospital readmission after stroke has dramatically increased since readmission became an established indicator of the quality of care. Stroke patients are considered as an important patient group contributing to readmissions and have been the main focus of many studies. Our study provides evidence that readmission after stroke is frequent also in a Norwegian stroke population, especially in the early phase following discharge, as more than half of our patients that were readmitted within one year presented during the first three months. Other studies vary slightly in the frequency of readmitted patients but show similar trends for the timing of readmissions.[102-105] The early phase after stroke might thus be regarded as a particularly vulnerable and unstable period. Regardless of the initial admission diagnose, it has been argued that the increased risk of readmission in the early phase after discharge may be caused by an acquired condition of vulnerability, a so-called "post-hospital syndrome".[150] During hospitalization, different stressors of physical, environmental and psychological nature may trigger pathophysiological and multi-systemic responses such as hypercatabolism, hypercoagulability, immunosuppression and increased sympathetic activity. This may cause progression of the disease that caused the hospital admission or trigger deterioration of comorbidities. Furthermore, new clinical or surgical conditions may emerge. This theory is based on the fact that many readmission causes often differ from what caused the initial hospitalization, and often include heart failure, pneumonia, other infection, gastrointestinal conditions, and metabolic derangements regardless of the original admitting diagnosis.[98, 150]

Table 3 summarizes readmission rates in other studies compared to the rates found in our studies. Although the reported rates from other studies vary widely in all periods, the NORSTROKE cohort is in the lower range of readmission. Large variations in readmission rates may occur due to differences in study populations, exposure, design, definitions used, and socioeconomic state of nations, and varying clinical practices.

Table 3. Readmission rates after stroke in other studies and in the NORSTROKE study

	Other studies	NORSTROKE
30 days	6.5 – 24.3 %	10.7%
90 days	17 – 35 %	18.8%
1 year	31 – 55 %	39.1%
5 years	67.5 – 83 %	69.3%

The table is a modified excerpt of readmission rates from several studies reporting 30-day readmission rates,[95, 102-104, 151-154] 90-day readmission rates,[102-105, 155] 1-year readmission rates,[102-105, 156-158] and 5-year readmission rates.[106, 113]

In our study, 10.7% of our ischemic stroke and TIA patients were readmitted within 30 days. Thirty-day readmission after stroke is a national quality indicator in Norway, and from 2014 to 2016, 11.4% of all Norwegian stroke patients aged 67 years or older were readmitted within 30 days.[4] In the same period, the readmission rates after pneumonia, heart failure or chronic obstructive pulmonary disease (COPD) ranged from 21% to 28%.[4] It might be that more stroke patients are discharged to nursing homes rather than to a home situation, leading to lower readmission rates than for some other conditions. The number of new patients presenting with readmission decreases in the period beyond one year after stroke.[113] Even though the majority of all readmitted patients in our study presented during the first year after discharge, more than half of all patients that survived for one year after stroke without any readmission were readmitted within five years. About 20% of all stroke patients are readmitted each year up to five years, but the number decline to 9% readmitted each year later than five years post stroke.[159] In 2017, Rohweder et al. published a study on readmission within ten years in 243 stroke patients from another Norwegian stroke center and found that the readmission rates stabilized and were almost similar to the distribution of readmission in the general population from year five to ten after stroke.[106] A possible explanation for why the readmission rates reach the background level of the general population after five years post-stroke might be that the most

severely affected patients, who have both the highest risk of readmission and the poorest long-term survival, are dead five years after the stroke.[160]

The most frequent causes of hospital readmission after stroke are infections, recurrent stroke, and other cardiovascular diseases.[105, 113] Our studies confirm that all of these are common causes of readmission after stroke, but we also show that stroke-related events, with the majority being stroke mimics or worsening of existing symptoms, is another common cause of readmission. Furthermore, we show that these causes are not only prevalent in the acute phase but remains important also in the long run.

Recurrent stroke and stroke mimics

Recurrent stroke was one of the top causes of readmission. The incidence, however, was low compared to studies on recurrent stroke incidence.[161, 162] In a meta-analysis of 13 studies, the pooled cumulative stroke recurrence risk was 3% at 30 days, 11% at one year, 26% at five years, whereas the incidences in our studies were almost half of this at the reported time points (Table 2).[162] Some evidence point to a decline in recurrent stroke incidence, which could explain these discrepancies. The meta-analysis found a temporal reduction in five-year recurrence from 32% in the 1960s to 16% in the early 2000s, and a Swedish study found a declining incidence of one-year stroke recurrence from 15% in 1998-2001 to 12% in 2007-2010.[162, 163] However, the most recent and largest meta-analysis to date found no significant decline in the risk of stroke recurrence after ischemic stroke or TIA.[114] In our study, 11.3% suffered a recurrent ischemic stroke within five years, which is comparable to the 9.5% found in a recent study including 3847 patients with minor stroke or TIA.[115] The combined five-year incidence of any recurrent stroke or TIA in our study was 13.8%, which is somewhat lower than 16.8% found in the other study, but the incidence of recurrent TIA was 8.3% in that study and only 2.0% in ours.

The average annual risk of recurrence after ischemic stroke or TIA is about 4.3%, with a particularly high risk during the first weeks which declines significantly over

time.[114, 161] We found a significantly higher risk of early recurrence in patients with LAA subtype, with 4.5% suffering a recurrent stroke within 30 days compared to the average 1.8%. Other studies have shown that the risk of recurrent stroke is almost doubled in patients with LAA up to one year after stroke.[144, 164] The reason for the increased risk of recurrence in patients with LAA is not fully understood, but the most likely explanation is that patients with LAA suffer repetitive shedding of thrombi from unstable atherosclerotic plaques triggered by shear stress in stenotic parts of the artery.[165] Also, cerebral ischemia may be induced by carotid surgery in some patients.[144] Both in our study and other studies, the distribution of recurrent stroke risk stabilizes among the stroke subtypes in the long-term perspective.[34, 166-168] This might nevertheless be influenced by age and mortality in a general stroke population, as the risk of recurrent stroke remains significantly increased in the long-term perspective when restricting the analyses to younger stroke patients.[169]

Many of the factors that were identified as risk factors for readmission in our studies, such as increasing age, previous vascular events, hypertension, ipsilateral large-artery atherosclerosis, and atrial fibrillation, are important risk factors for recurrent stroke.[91, 115, 163] A study on one-year recurrence in almost 200, 000 Swedish patients with ischemic stroke between 1998 and 2009 found that warfarin treatment for atrial fibrillation, lipid-lowering medication, and antithrombotic therapy reduced the risk of recurrent stroke.[163] Accumulating evidence shows the clear benefit of antiplatelet medication, anticoagulation, blood pressure control, and lipid-lowering drugs. Clinical trials on secondary prevention have demonstrated risk reductions in stroke recurrence of 27% for antihypertensive treatment,[70] 16% for lipid-lowering medications,[71] 30% for antiplatelet medication,[170] and 68% for anticoagulation treatment.[80] However, the largest meta-analysis in the field of recurrent stroke found no significant decline in the stroke recurrence rate despite considerable improvement in secondary prevention with medical treatment and a reduction in stroke risk factors.[114] This implies that there still exists room for improvement, especially when it comes to insurance of adherence to medications and compliance. Furthermore, even

though it is challenging to implement lifestyle changes, this is highly important in younger stroke patients.

Educational campaigns in Western Norway have led to a higher recognition of conditions that could represent stroke.[171] One should have a low threshold for admitting patients with sudden onset of neurological symptoms, including patients with previous stroke that experience worsening of or new neurological symptoms due to their high risk of recurrent stroke.[113] Readmissions due to events related to the initial stroke were common during all periods measured in our studies. During the first month after discharge, a high number of patients were readmitted with possible stroke where the symptoms were evolving stroke, aggravation of existing neurological deficits or stroke sequela. The few studies that have reported the number of patients readmitted with stroke-related events have found that such conditions are important contributors to readmissions within the first year after stroke.[95, 103, 172] Distinguishing between stroke and stroke-like syndromes is difficult, and stroke mimics (false-positive stroke diagnosis) represents approximately 50% of all patients admitted with suspected stroke.[173] Increasing stroke severity has been related to the risk of readmission with neurological sequela after stroke.[172] Experience from clinical practices suggests that in situations where older and disabled patients that have previously suffered a stroke present with a slight worsening of stroke sequela, there is a larger possibility that the symptoms are caused by other conditions than stroke, like infections, sleep-disturbances, or adverse effects of medications. Retrospectively one could suggest that some of these readmissions could have been avoided. However, a reduction in the stroke mimics rate could potentially lead to an increase in the number of underdiagnosed stroke cases.[173] Even though it would remove some pressure on the hospitals if one could avoid some hospital readmissions or admission related to stroke mimics, a low threshold for admitting patients with acute onset of neurological symptoms should be valued, and it is highly uncertain whether it would be beneficial to avoid such readmissions even though the final diagnose is not recurrent stroke.

Vascular events and cardiac disease

Recurrent ischemic stroke was considerably more frequent than myocardial infarction in our study, with an incidence of myocardial infarction of 0.3% at 30 days and 6.9% at five years. This finding is consistent with both randomized clinical trials and population-based studies.[161, 174, 175] In 2018, a meta-analysis including 58 studies on recurrent stroke, myocardial infarction and vascular deaths in patients with ischemic stroke or TIA between 1976 and 2014 found an annual risk of myocardial infarction after ischemic stroke or TIA in 1.7%, and 3.6% in patients with known coronary artery disease.[114] In addition to coronary artery disease, male sex, hypertension, and peripheral artery disease were identified as risk factors for myocardial infarction after ischemic stroke or TIA. The study also found a temporal decline in myocardial infarction after stroke, as stroke patients enrolled in studies later than 2005 had an annual risk of myocardial infarction of 0.9%. Similar trends have been demonstrated in the general population.[176] The reduction in myocardial infarction after stroke is likely caused by a decline in the prevalence of cardiovascular risk factors and better treatment of modifiable risk factors.[114, 176]

In 1998, the AHA/ASA published a statement suggesting that atherosclerotic stroke should be considered as a high-risk condition for atherosclerotic coronary events and included in risk prediction tools for cardiovascular diseases.[118] The number of studies reporting on stroke subtypes and the risk of myocardial infarction is low, but overall, no difference between the stroke subtypes has been demonstrated.[114] In our study, the highest incidence of myocardial infarction at five years was found in patients with LAA, but neither did we show any differences between the stroke subtypes. Some studies have found that LAA subtype is associated with a generally increased risk of new vascular events, including both stroke, coronary artery disease and peripheral artery disease.[177, 178] Atherosclerosis is a systemic disease and a shared mechanism for coronary artery disease, peripheral artery disease, and atherosclerotic stroke subtype. However, studies show conflicting results between stroke subtype, the prevalence of cardiovascular risk factors, and the risk of new vascular events.[30, 32, 33, 115] This suggests that the stroke subtypes should have the same preventive strategies based on

their presence of vascular risk factors, and that assessment of traditional cardiovascular risk factors and concurrent coronary artery disease and peripheral artery disease to determine the atherosclerotic burden might be helpful in predicting the risk of new vascular events in patients with ischemic stroke or TIA.[178]

Cardiac disease, including myocardial infarction, represented about 12% of all readmissions within 30 days, and 11% of all first readmission within one year in our studies. At five years, almost 21% had been readmitted due to cardiac disease. Besides from myocardial infarction, arrhythmias and congestive heart failure were the most common cardiac diseases causing readmissions, with five-year incidences of 7% and 5%, respectively. Both were significantly more common in patients with CE subtype, which had an overall increased risk of readmission due to heart disease at both 30 days and five years. The relationship between cardioembolic stroke and readmission due to cardiac disease is clear, as these patients have an underlying cardiac disease which caused the ischemic stroke or TIA. Furthermore, CE subtype is associated with high age,[32] and the occurrence of both arrhythmias and congestive heart failure increases with age.[179, 180] Patients with stroke are at increased risk of readmission with heart failure compared to the general population, and about 3-5% of ischemic stroke patients are readmitted with heart failure annually.[105, 113]

Readmission due to venous thromboembolism (VTE) was a rare event in our cohort, with a five-year incidence of only 1.6%. The risk of VTE is especially high during the first weeks after ischemic stroke and TIA, probably due to immobilization and enhanced activity in the coagulation system.[119] About 0.4% of the patients in NORSTROKE develop either DVT or pulmonary embolism during the index admission, and only 0.2% of our patients were readmitted with VTE during the first 30 days. In a Norwegian study of 489 stroke patients, DVT or pulmonary embolism occurred in 0.6% each during the first week after stroke onset.[181] However, the true incidence of VTE both during the index admission and after discharge is probably higher. A prospective study including 102 ischemic stroke patients found that 3% developed clinical DVT and 5% developed clinical pulmonary embolism within 21 days, but VTE was detected in 40% by use of MRI direct thrombus imaging.[182]

Furthermore, half of the clinically evident VTEs were overlooked by the attending team.[182] Venous thromboembolism was previously one of the most frequent complications of ischemic strokes, but with increasing attention towards early mobilization and more frequent and effective use of antithrombotic prophylaxis in high-risk patients, the rates of symptomatic VTE have declined.[182]

Infections

Infection was the most frequent cause of readmission after five years in our study, and also a dominating cause of readmission during the first months after discharge. Other studies show that infections are the cause of 12-34% of early readmissions and 15-44% of all readmissions within one year.[95, 103, 104, 158] We found that infections caused 17% of all first readmissions after ischemic stroke and TIA during the first 90 days and 19% within one year. After five years, about 30% had been readmitted with an infection, with an especially high proportion during the first 30 days. The high vulnerability of infections in the early phase after stroke can relate to acute stroke-induced immunosuppression or the hospitalization with nosocomial infections and physical insults like urinary catheterization and mechanical ventilation. In some cases, early infections may also have been acquired before stroke onset, with a subsequent worsening of symptoms after stroke onset.[183]

Most post-stroke infections in our studies involved the urinary tract or the respiratory system. Pneumonia and urinary tract infections (UTI) occur in approximately 10% of stroke patients in the acute phase each and continue to affect stroke patients in the long-term perspective.[93, 107] Within five years, 15% of our patients had been readmitted with pneumonia, and 9% had been readmitted with UTI. Shared risk factors for post-stroke pneumonia or UTI are increasing age and severe strokes.[110, 183, 184] Male sex is associated with post-stroke pneumonia, whereas female sex is associated with post-stroke UTI.[110, 183, 184] Urinary catheterization increases the risk of UTI and should be avoided if possible, or removed as soon as possible or replaced by intermittent catheterization or other alternatives.[185] Factors associated with post-

stroke pneumonia are use of a nasogastric tube or mechanical ventilation, diabetes mellitus, chronic obstructive pulmonary disease, and smoking.[183] The most consistent risk factor for developing pneumonia after stroke, however, is dysphagia, increasing the risk by a three-fold.[183, 186] Dysphagia with secondary aspiration is thought to be the cause of most pneumonia occurring after a stroke. Depending on the diagnostic technique, dysphagia occurs in 37% to 78% of all stroke patients, half of whom aspirate.[186, 187] Formal screening for swallowing difficulties and appropriate dietary modifications are therefore important to prevent post-stroke pneumonia.[188] Most patients with swallowing difficulties have spontaneous improvement in swallowing function, but dysphagia can also be long-lasting.[189] Although nasogastric tube or percutaneous endoscopic gastrostomy should be provided in patients with dysphagia due to nutritional reasons, neither offers any protection against aspiration pneumonia.[190] Prolonged use of nasogastric tube may have an adverse effect and should be replaced by a percutaneous endoscopic gastrostomy in individuals who remain unable to swallow. Furthermore, the use of prophylactic peptic ulcer medications after stroke have been associated with hospital-acquired pneumonia and should perhaps be avoided in patients who are not at high risk of developing peptic ulcers.[191]

Several studies have investigated the effect of prophylactic antibiotic treatment.[192-195] In a Cochrane review from 2018 including eight randomized controlled trials on prophylactic antibiotic treatment in stroke patients, the overall occurrence of infection fell from 26% in the control groups to 19% in patients that received prophylactic antibiotic treatment.[196] The decline was mainly driven by a reduction of UTIs, and no effect was found on the prevention of pneumonia. To date, no studies have shown a beneficial effect of prophylactic antibiotic treatment on functional outcome or mortality, and prophylactic treatment is not recommended for any subgroups of stroke patients.[185, 192, 194, 196]

Fractures

We found that readmission with fracture was more common in the phase beyond the first six months. This has also been demonstrated in other studies.[105, 106, 129, 197] In two large studies from the UK, about 10% of stroke patients had been admitted with a fracture within ten years.[136, 198] The incidence of patients readmitted with fractures was considerably higher in our study, as about 12% had been readmitted with any fracture within five years. Furthermore, some types of fractures are usually treated in primary care and do not require hospitalization, and the true incidence of any fractures in our population is likely higher. The rate of hip fractures in Norway, which is a serious condition with high mortality in the elderly, is among the highest in the world.[199, 200] Hip fractures usually require hospitalization, and almost 7% had been readmitted with hip fracture within five years in our study. The reason for the high occurrence of fractures in Norway and Scandinavia is probably multifactorial, but not fully understood. As stroke patients have considerably increased rates of fractures compared to the general population, careful assessment for risk of falls and treatment of osteoporosis is crucial in stroke patients.[113, 129, 197] Prevention of falls require multifactorial risk assessment and simultaneous management with exercise to improve mobility.[201] Early mobilization is also important to prevent increased bone resorption after stroke. A small Norwegian study of 40 patients found significant differences in bone mineral density in stroke patients who learned to walk within one year after stroke.[202] Vitamin D2 supplementation can be useful for fall-prevention in stroke patients as it might reduce muscle atrophy, and supplementation with bisphosphonates increases the bone mineral density after stroke.[131, 203, 204] Calcium is a major component of bone, and sufficient intake of calcium is recommended for prevention of osteoporosis; however, studies show conflicting results on its effectiveness for prevention of fractures in stroke patients, and there have been concerns that calcium supplementation might have adverse cardiovascular effects.[205, 206] A final medical approach for reducing hip fractures is supplementation with folate and vitamin B12, which showed beneficial effects in the risk of fractures in a randomized controlled trial of 628 elderly Japanese stroke patients.[207]

Seizures and epilepsy

The long-term risk of post-stroke epilepsy after ischemic stroke ranges from 2% to 5%.[126, 128, 208] The five-year incidence of readmission with seizure or epilepsy was 4.3% patients in our cohort, which is higher than the 3.1% patients that developed epilepsy in another Norwegian study of 484 ischemic stroke patients followed for 7-8 years.[127] We do not know the exact amount of patients diagnosed with epilepsy in our cohort, as secondary diagnoses and medical treatment have not been included in our studies, and some patients may have been referred to the outpatient clinic.

Post-stroke epilepsy has traditionally been defined as two or more unprovoked seizures occurring later than one week after an ischemic stroke; however, according to the new definition from the International League Against Epilepsy, epilepsy can be diagnosed after a single unprovoked seizure if other findings support that the risk of further seizures equals the risk seen after two unprovoked seizures over the following ten years (at least 60%).[209, 210] Even though stroke patients in general have a relatively low risk of seizures and none of the identified risk factors for post-stroke epilepsy are strong enough to initiate prophylactic AED treatment, this category may apply to some stroke patients with late unprovoked seizures according to the new definition.[128, 211]

Gastrointestinal bleeding

Gastrointestinal (GI) bleeding was previously among the more common complications after stroke, occurring in about 3-5% during stroke hospitalization, but newer studies report lower rates of about 1.5%.[2, 137, 138] The five-year incidence of readmission with GI bleeding was 4.4% in our cohort. A case-control study found that 5.2% of ischemic stroke patients were readmitted with GI bleeding within five years, whereas only 1.4% of patients without stroke were admitted with GI bleeding during the same period.[113] Stroke patients are at higher risk of GI bleeding than non-stroke patients due to treatment with anticoagulants or antiplatelet therapy and shared

factors for ischemic stroke and GI bleeding.[212, 213] About half of all GI hemorrhages in stroke patients are severe.[2, 137] Post-stroke GI bleeding is associated with higher rates of dependency and mortality, which might relate to the immediate consequences of the bleeding, but also to other factors associated with post-stroke GI-bleeding, such as high age, severe stroke, cancer, and sepsis.[137, 138] Other factors that are associated with post-stroke GI bleeding are history of peptic ulcers and hypertension, whereas preadmission use of antithrombotic treatment or proton pump inhibitors or thrombolytic treatment are not.[90, 137, 138]

The impact of stroke subtype on readmission after stroke and TIA

Our studies demonstrate that readmission after stroke varies among the different subtypes. LAA and SOE subtype were associated with the highest risk of readmission within 30 days, whereas CE subtype had the highest risk of readmission at five years. SOE subtype was associated with a lower risk of readmission within five years. Few other studies on readmission after stroke have included ischemic stroke subtype.[95, 104, 214, 215] A retrospective study of 265 ischemic stroke or TIA patients found no difference in the risk of 30-day readmission among the stroke subtypes, whereas a study of 987 young stroke patients included in the late 1980s and followed until 2009, found a significantly increased risk of readmission for the CE subtype.[214, 215] Other studies have reported that LAA or CE subtype independently increases the risk of 30-day readmission and that the CE subtype increases the risk of one-year readmission.[95, 104] All of these studies were, however, smaller than ours, and to our knowledge, our cohort is the largest to date where the risk of readmission has been investigated by stroke subtype.

Differences in the rates and risk of readmission among stroke subtypes are reflected in the frequency of different causes of readmission. The high occurrence of recurrent stroke and stroke-related events within 30 days associated with LAA and SOE subtype probably explains why these patients had a higher risk of 30-day readmission. The same accounts for patients with CE subtype, which had higher risks of readmission with cardiac disease at five years, and high rates of infections, fractures, seizures, and stroke-related events. CE subtype is associated with high age, severe strokes, and poor outcome, which subsequently can increase the risk of infections, fractures, and seizures after stroke.[32, 33] The underlying cardiac disease naturally increases the risk of readmission with cardiac disease, and blood pressure alterations may lead to falls and fractures.[216] Since the 1980s, the rate of stroke caused by CE has tripled, and are projected to increase further.[217] As our results as well as the results from other studies show that CE strokes carry a high risk of poor outcome with hospital readmission and death, early diagnosis together with

appropriate treatment and careful monitoring and handling of patients with CE is crucial.[178, 215, 218]

Stroke etiology combined with differences in risk factor profile and stroke severity likely predispose for different diseases at various degrees. It is possible that factors not investigated in our studies may explain the detected differences in rates and causes of readmission after ischemic stroke and TIA. Our results need validation from other studies, but they suggest that stroke subtype may provide useful information on the risk of new diseases after stroke.

Risk factors for hospital readmission after ischemic stroke and TIA

Risk factors for hospital readmission after stroke is a disputable topic investigated by many studies with differences in study population, study design and length of follow-up. Despite the limited comparability between studies, some factors are repeated, including age, increasing stroke severity, functional disability, longer hospital stay, diabetes mellitus, and an increasing number of hospitalizations prior to the stroke admission (Table 4). It is plausible that risk factors related to early readmissions after stroke may differ from risk factors for readmission in the subacute and chronic phase, as complications and provided health care may to a larger extent contribute to early readmissions, whereas readmissions beyond the acute phase may relate more to comorbidity in stroke patients. However, our studies provide evidence that many of the factors associated with readmission in the acute and subacute phase, such as increasing age, poor functional outcome, atrial fibrillation and atherosclerotic disease in other sites than the cerebrovascular one, is also associated with readmission in the chronic phase of stroke.

Table 4. Risk factors for hospital readmission after stroke

Country, Author, Year	Data Source	Study type, year included	No. of patients	Follow-up	Predictors
Taiwan, Chuang,[219] 2005	Patient interviews	Prospective cohort, 1999-2000	489	30 days	Number of limitations in activities of daily living, first incidence stroke, need of wound care, adoption of a care plan, discharged home with full-time helper or family care
USA, Bhatta-charya,[214] 2011	Medical records	Retrospective cohort, 2009-2010	265	30 days	Coronary artery disease
USA, Lichtman, 2013	Administrative data	Retrospective cohort, 2005-2006	307 887	30 days	Increasing age, female sex, diabetes mellitus, heart failure, prior acute coronary syndrome, peripheral artery disease, anemia, protein malnutrition, renal failure, pneumonia, dementia
Australia, Kilkenny,[140] 2013	Medical records	Retrospective cohort, 2000-2010	3328	28 days	Dependent premorbid functional status, adverse events during index admission
USA, Fehnel,[102] 2015	Administrative data	Retrospective cohort, 2008	39 178	30 days	Bowel incontinence, feeding tube, COPD, heart failure, pressure ulcer grade 4, renal disease
USA, Shah,[95] 2015	Patient interviews and medical records	Prospective cohort, 2012-2013	505	30 days	CE or LAA subtype, any medical complication
USA, Strowd,[220] 2015	Administrative data and medical records	Retrospective case-control	165 cases, 85 controls	30 days	Increasing stroke severity, increasing number of prior hospitalizations in the year before stroke, hyperlipidemia
USA, Mittal,[152] 2017	Medical records	Prospective cohort, 2007-2011	537	30 days	Discharge to nursing home (negative)
USA, Nouh,[221] 2017	Registry data and medical records	Retrospective case-control, 2013-2014	1544	30 days	Index admission to a non-neurology service
USA, Vahidy,[222] 2017	Administrative data	Retrospective cohort, 2013	319 317	30 days	Recanalization therapy (negative)

USA, Crispo,[223] 2018	Administrative data	Retrospective cohort, 2014	439 682	30 days	≤ 40 years, ≥7 comorbidities, adverse medication-related event, length of stay >1 week, leaving the hospital against medical advice, admission to a large hospital, public health insurance
Taiwan, Li,[224] 2011	Administrative data	Retrospective cohort, 2006-2007	1194	1 year	Increasing age, diabetes mellitus, longer length of stay, continuous use of antiplatelet therapy less than 9 months
Taiwan, Lin,[103] 2011	Medical records and patient interview	Prospective cohort, 2006-2008	2657	1 year	Increasing age, prior TIA/stroke, atrial fibrillation, coronary artery disease, any complication, longer length of stay, dependency at discharge
Australia Kilkenny,[225] 2015	Registry data and administrative data	Prospective cohort, 2009-2010	782	1 year	≥2 emergency department presentations before the index admission, higher Charlson Comorbidity Index score, TIA on index admission
Portugal, Leitao,[104] 2016	Medical records	Retrospective cohort, 2013	480	1 year	Increasing stroke severity, ASPECTS score <7, cardioembolic etiology, thrombolysis (negative)
Taiwan, Hsieh,[172] 2017	Administrative data	Retrospective cohort, 2000-2012	10 877	1 year	Age, male sex, increasing stroke severity, any complication, number of admission the past year, modified Charlson Comorbidity Index, hyperlipidemia, neurologic service (negative)
Canada, Caro,[226] 2006	Administrative data	Retrospective cohort, 1990-1995	18 704	5 years	Age >65 years, male sex, atrial fibrillation, heart failure, angina, prior myocardial infarction, hypertension, previous TIA, previous stroke (negative)

Age was the most consistent risk factor for readmission in our studies, increasing the risk of readmission about 2-3% for each aging year. As the majority of stroke patients are 75 years of age or older, one can argue how useful age is in predicting the risk of readmission.[5] However; it implies that for each tenth aging year, the risk of readmission increases between 20-30%. With aging comes a gradual decrease in

physical and mental capacity and a growing risk of disease and an increased risk of several conditions at the same time, and a decreased ability to compensate for acute diseases.

Hypertension, coronary artery disease, and peripheral artery disease were associated with readmission in both the subacute phase and in the chronic phase. These are also consistent factors for readmission in many other studies (Table 4). Hypertension is one of the main risk factors for stroke and cardiovascular disease, and coronary artery disease and peripheral vascular disease are manifestations of systemic atherosclerosis. Presence of these conditions increased the risk of readmission as recurrent stroke and cardiac disease were among the top causes of readmission. Special attention towards optimizing management of other underlying medical conditions, especially hypertension, coronary artery disease, and peripheral vascular disease, might thus be helpful to reduce readmissions after stroke. Hypertension is probably the most important modifiable risk factor, and systolic and diastolic blood pressure reduction is linearly related to a lower risk of recurrent stroke, myocardial infarction, all-cause mortality, and cardiovascular mortality after stroke.[70] We did not find that prescription of treatment with antihypertensive treatment, platelet inhibitors, anticoagulation or statins affected the risk of five-year readmission. However, as we do not have information on medical treatment after discharge in patients that were not readmitted, we cannot conclude that such treatment was ineffective.

Increasing comorbidity is among the most consistent risk factors for readmission in stroke patients, as well as in the general population.[139, 140, 172, 223] Many other studies have included general comorbidity scores, such as the Charlson Comorbidity Index (Table 4), but we did not have sufficient information to generate a general comorbidity score. However, the risk factor burden, which was constructed from six traditional cardiovascular risk factors, has been associated with an increased risk of recurrent stroke.[145] We found that an increased risk factor burden was significantly associated with readmission in the subacute phase, and although we did not include risk factor burden in the multivariate analyses of other time-intervals due to

collinearity with other included variables, readmitted patients had a higher risk factor burden than patients that were not readmitted.

Poor functional outcome was an independent risk factor for readmission both in the subacute and chronic phase in our studies. We also found that patients readmitted early tended to have poorer functional outcome than those who experienced the first readmission later. Neurological deficits and the functional outcome often improve during the first year after discharge, and the predictive value of the short-term mRS score in our study may thus be limited. Almost 65% of all Norwegian stroke patients have an mRS score of 0-2 after three months.[51] The post-stroke functional outcome depends on stroke severity and premorbid function, which has been associated with early readmission after stroke.[140] We found that more patients readmitted within five years received home nursing before the stroke, but more of the patients that were not readmitted within five years were permanently institutionalized prior to the ischemic stroke or TIA. Poor post-stroke functional outcome has been associated with readmission in some studies, but most studies usually include stroke severity rather than functional outcome, which is consistently associated with readmission (Table 4). Patients that were readmitted had more severe strokes than patients without readmission in all our studies, but due to collinearity with functional outcome and generally low NIHSS scores compared to other studies, we did not include stroke severity in the multivariate analyses. We do not have a good explanation for the low NIHSS score in our population, but the same trends are observed in the national Norwegian stroke registry, where about 65% of all patients have an NIHSS score of 5 or less, and 41% have an NIHSS score of 2 or less.[51] The average NIHSS score may also be affected by the inclusion of TIA patients and exclusion of patients that died before discharge or were discharged to palliative care. The low stroke severity in the Norwegian population may be a result of national population-based stroke campaigns and that the hospitals have a low threshold for admitting patients with acute neurological symptoms. Furthermore, 94% of all Norwegian stroke patients are treated in stroke units, which has been documented to improve functional outcome in stroke patients.[51, 227]

Although complications are most common in patients with severe strokes and generally poor outcome, it remains a risk factor for readmission after adjusting for such confounders.[103, 140, 172] In our analysis, complications during index admission were associated with 30-day readmission in univariate analyses, whereas enteral feeding was the only complication that was an independent risk factor for 30-day readmission. Enteral feeding is associated with an increased risk of pneumonia, gastrointestinal bleeding, and also indicates more severe strokes. Pneumonia or urinary tract infection during the index admission significantly increased the risk of readmission with the same infection within 90 days. In a recent study from the 2013 National Readmission Database in the US, 29% had an infection during the index admission, and the odds of an unplanned 30-day readmission was 23% higher in patients with infections.[228] The study also found that only 14% of the stroke patients that were readmitted for an infection did not have an infection during the index admission.[228] We found that complications were more frequent in patients readmitted early. A likely explanation is that patients with complications have more severe strokes which increases the risk of readmission, and that complications have an adverse impact on the functional outcome. It is also likely that some of these patients are predisposed to certain infections. However, some of the readmissions might be directly related to the complication, and some patients may have been discharged too early.[95]

The length of stay is affected by many factors including stroke severity, pre- and post-stroke function, and occurrence of complications. Shorter length of stay have been associated with an increased risk of 30-day readmission in elderly Norwegian patients.[229] However, longer length of stay have been associated with readmission after stroke in several studies (Table 4). A possible explanation for this might be that patients with long hospitalizations have more severe strokes and more complications. We found no difference in the length of stay between readmitted and not readmitted patients in any of our studies. A reduction in the length of stay in Norwegian hospitals has been observed after the implementation of the Norwegian Care Coordination Reform (Samhandlingsreformen) in 2012, but there has also been a slight increase in the overall 30-day readmission rate.[99] The focus on rapid discharge

after complete evaluation and treatment might have led to some premature discharges. Despite that many readmissions are unavoidable, awareness and proper care during the stroke admission, despite causing longer hospitalizations, would be a better alternative than rapid discharge and early readmission.

Patients with ischemic stroke are usually considered having a worse prognosis than patients with TIA, but TIA patients had the same risk of readmission as patients with ischemic stroke in our studies. There are conflicting results whether TIA patients have lower, similar or higher rates of readmission than ischemic stroke patients, which could be due to differences in use of secondary prevention and adherence to medical treatment.[157, 214, 225] TIA patients have the same risk factor profile and underlying causes of their ischemic event as patients with ischemic stroke, and likely the same risk for many diseases despite no permanent neurological dysfunctions. This emphasizes the importance of attention towards comorbidity and aggressive and accurate secondary treatment in order to reduce readmissions after TIA.

In 2013, Lichtman and colleagues published a retrospective cohort study of about 300 000 ischemic stroke patients. Based on predefined criteria for preventable readmissions, they found that 1.7% of all discharges were followed by preventable readmissions within 30 days, representing 12% of all readmissions within 30 days. Preventable readmissions were associated with high age, female sex, cardiovascular comorbidity, pneumonia, dementia, anemia, and malnutrition.[230] Another study found that increasing comorbidity, insurance type, and mental illness were associated with potentially preventable readmissions, which represented 8.4% of all 30-day readmissions after stroke.[231] Some of the factors that we have found to be associated with readmission, such as age and history of atherosclerotic disease, are hard to influence, but other factors like acute complications, hypertension, atrial fibrillation, and possibly functional outcome, are modifiable and can be targeted to improve both early and late readmissions.

The impact of hospital readmissions on mortality

Hospital readmission has been hypothesized a risk factor for death after stroke. In our study, readmission within 30 days was an independent risk factor for death within one year after stroke. This finding is consistent with that of a large US study, and smaller studies have also found similar trends.[3, 152, 232] In paper IV we demonstrate that a significantly higher proportion of patients readmitted within five years had died, compared to those who had not been readmitted. Readmissions later than 30 days after discharge probably also affect mortality. This was shown in a study of 356 patients with intracerebral hemorrhage in Portugal, where readmission within one year led to a five-fold increase in two-year mortality.[233] A reason for the mediating effect readmission has on mortality might be that post-stroke complications requiring hospital readmissions lead to higher disability. Less severe complications, such as urinary tract infections and simple fractures can be treated in primary health care, while more severe complications require hospitalization. Pneumonia, sepsis, vascular events, heart failure, and hip fractures were all frequent causes of readmission, and all increase the post-stroke mortality.[90, 112, 234] Another reason for the increased risk of mortality in patients that are readmitted early after stroke might be that an unplanned hospital admission can interfere with rehabilitation, and delay, reduce or even inhibit recovery after stroke. A third explanation that also interferes with the two other explanations might be that the stroke patients that are readmitted have a worse prognosis already at the index admission. It might be that with declining in-hospital mortality, patients that previously would not have survived the hospitalization are now discharged alive. Furthermore, these patients might be older, more disabled, and fragile, all of which are associated with increased mortality. Several risk factors for post-stroke readmission also increases the risk of death, such as high age and severe stroke. Thus, readmission and death might be correlated in the sense that the stroke patients that have the highest risk of readmission, also have the highest risk of death.

Future perspectives - preventing readmissions

Reducing hospital readmissions requires complex, multifaceted and validated strategies, all of which still needs to be further explored. Reducing hospital readmissions has become a top priority in the United States after the Hospital Readmissions Reduction Program was established in 2012. The program financially penalizes hospitals with a higher than expected risk-standardized 30-day readmission rate.[235] The program has led to a decline in 30-day readmission rates from 21.5% in 2007 to 17.8% in 2015 for the targeted conditions, whereas readmission rates in non-targeted conditions declined from 15.3% to 13.1%.[236] However, the program has received criticisms both for disproportionally penalizing hospitals that care for vulnerable populations and increasing post-discharge mortality, as recent studies have found an increase in 30-day and one-year mortality after pneumonia and heart failure simultaneously with the decrease in 30-day readmission rates.[235, 237-239]

Use of prediction tools could help target the delivery of health services, and contribute to reducing the number of readmissions.[139] Prediction tools could either be based on readmission risk regardless of the initial admission cause, or disease-specific prediction tools such as the risk of readmission after stroke. One could also use prediction tools for all-cause readmission, or prediction tool for specific causes of readmission. Increasing age, disease severity, prior healthcare utilization and complications during index admission are associated with both generic and disease-specific readmissions, but in order to deliver specific initiatives to prevent readmissions, I believe that a disease-specific readmission-reduction predictive tool, especially in the case of stroke, would be most valuable.[139] Although many prediction tools have been developed for identifying patients at higher risk of readmission regardless of the disease and the readmission cause, most of them lack validation.[139]

Another strategy for reducing readmissions, especially in the vulnerable immediate post-discharge period, regards transitional care.[240, 241] Transitional care refers to a set of actions developed to ensure the coordination and continuity of health care when a patient moves from one health care setting, for example a hospital, to another health

care setting, such as home or a nursing home.[240, 242] Important care-transition strategies to reduce hospital readmissions include patient education, proper discharge planning, medication reconciliation, scheduling follow-up appointments, follow-up phone calls, and home visits.[241] Such interventions proved useful in a quality improvement project on stroke patients, with a subsequent reduction of 30-day readmission rates from 9% to 3% and a reduction from 16% to 12% in emergency department visits.[243] Urgent and unplanned transitions increase the risk of medication errors, inadequate communication between health care providers, and discharge to environments not capable of meeting the patients' medical needs. A strategy to prepare patients for the life after discharge is the education of eligible patients about relevant diagnoses such as stroke risk factors and warning signs, prevention of infections, and attention towards fall-traps, and the importance of self-care and obtaining and taking prescribed medication and medication management.[244] Another strategy is scheduling follow-up appointments with both primary care providers and outpatient neurological clinics. Hospitals often rely on quick follow-up by primary care providers for monitoring newly discharged patients, and the discharge paperwork often instructs the patient and primary care provider to schedule follow-up appointments. However, patients can be unable to schedule follow-up appointments quick enough, or there may be limited capacity in primary care. A retrospective cohort study including 78 345 elderly ischemic stroke patients discharged home found that early primary care visits or neurology visits led to a small, but significant, reduction in 30-day readmission.[245] Furthermore, a clinical trial from Denmark with 155 stroke patients discharged home with persistent disability and impairment, demonstrated significant reductions in six-month readmission rates for patients receiving follow-up home-visits by a physician or instructions from a physiotherapist compared to patients that received standard aftercare (26% and 34% versus 44%).[246]

Readmissions are often unrelated to the initial admission as readmission may represent a progression in the natural history of underlying diseases and comorbidity.[98] It is therefore important to remember that not all readmissions are preventable. Usually, readmissions are considered preventable if clinically related to a prior admission.[247] Some studies have defined preventable readmissions as

readmissions related to predefined causes such as infections, COPD, hypertension, diabetes mellitus, heart failure, and dehydration,[230, 231] whereas others have reviewed the medical records for determination of readmissions that could have been avoided.[152, 248] Between 2% and 31% of all unplanned readmission within 30 days have been considered preventable.[152, 230, 231, 248] However, the retrospective nature of these studies and the use of administrative data together with predefined categories of preventable causes limits the generalizability and impact of these studies. In relation to our findings, many of the most frequent causes of both short-term and long-term readmission may be potentially preventable, such as fractures, infections, and thromboembolism.

A final aspect is the question on when to stop treating patients. Many stroke patients are old, multimorbid, fragile, and cognitive and physically impaired. Some of these patients may be better served by good palliative care rather than being readmitted for treatment at hospitals. It is not possible to give clear directions on scenarios where this applies, but good communication between patients, their families and the health care providers is essential, especially towards the end of life.

Although readmission rates will never be zero, the current frequency of readmission includes many readmissions that could be prevented by improving care and initiate measures in patients at highest risk of readmission. Successful recovery after stroke requires that health care professionals also address other factors, such as comorbidity and care.[150] Hospitals have limited control of care after discharge, so strategies to reduce readmission both in the acute and chronic phase must be multidisciplinary and involve health care professions in both secondary and primary care. All of the mentioned strategies to reduce readmission would be time-demanding in a system already under high pressure. Even though a minority of readmissions are preventable when reviewed retrospectively, intervention studies show promising results. If we could lower the readmission rates, it would release some of the pressure on the health care system, and be highly beneficial for the patients.

Strengths and limitations of the thesis

Our studies have several limitations that deserve attention. All the included studies are registry-based, which thus can lead to either underestimation or overestimation of readmission rates after stroke. In our case, it is likely that we may have underestimated the readmission rates, because it is inevitable that some patients have been readmitted to hospitals outside the region of the Western Norway Regional Health Authorities. Our 30-day readmission rate largely resembles what has been found for 30-day readmission after stroke in the Western Norway Regional Health Authorities in the reports by the Norwegian Institute of Public Health, and we believe that few patients have been missed from our early-readmission rates.[4] It is more likely that we have lost some readmissions happening beyond the first 30 days, which may have led to an underestimation of the long-term readmission rates. On the other side, we may also have overestimated the long-term incidences of readmission, as the Kaplan-Meier method is a survival model originally designed to investigate mortality over time. When the outcome of interest is different from all-cause death, such as in the case of readmission, mortality is a competing risk which can preclude the occurrence of readmission and lead to biased results.[249] However, most studies investigating readmission with survival models have used Kaplan-Meier estimates and the Cox regression, easing the comparison between studies.

A second limitation of using registry-based data is the lack of necessary information, which may result in confounding. The process of hospital readmission is multifactorial and may involve patient, family, health care system, and even environmental factors. It is inevitable that some factors in the process of readmission are not included in our study, for example medical compliance after discharge and long-term disability. Furthermore, medical records are not designed for research purposes, which may result in misclassified or unavailable data in some readmission cases.

A third limitation lies in the TOAST classification, which has well-documented value but a high proportion of patients classified as stroke of undetermined cause.[33, 35]

Furthermore, the TOAST classification is not up to date on the recent technological advances, and many of the newer classification systems may be more appropriate in a clinical setting. However, the newer classifications depend on the availability of modern diagnostic technology, and some of them are not appropriate for research as there are too many subtypes.[25]

A strength of our study is the ascertainment of data related to readmissions made by review of medical records, and the relatively large study population prospectively investigated according to a predefined protocol with a comprehensive collection of data. Although we cannot exclude that some individuals suffering ischemic stroke or TIA were not admitted to our hospital and thus not included in the NORSTROKE registry, the population-based design with the exclusion of patients living outside the local area of Haukeland University Hospital limits the influence of a selection bias. However, the generalizability of our studies is limited as a result of the single-hospital design. Furthermore, all patients were treated in a stroke unit, which may lead to a better outcome and consequently lower readmission rates than studies including patients not treated in stroke units. Our cohort is small compared to many other studies investigating readmission, but most of these larger studies use administrative data for both identifying the cohort and readmissions, and many only include clinical patient-level data other than medical comorbidity and demographic data.[141]

Conclusions

We showed that the large majority of our ischemic stroke and TIA patients were readmitted within five years. More than one-third of our patients were readmitted within one year after discharge, with half of the readmissions occurring within the first 90 days. The top causes of readmission in both the acute and chronic phase were infections, stroke-related events, recurrent stroke or TIA, and cardiac disease. Fractures were another frequent cause of readmission in the chronic phase.

We showed that most risk factors for readmission in the acute phase remained important long-term. These included increasing age, poorer functional outcome, atrial fibrillation, hypertension, and atherosclerosis in other sites than the cerebrovascular one. Patients readmitted early had more complications during the index admission and a poorer functional outcome than patients readmitted later after discharge. Our results indicate that rapid and good acute treatment in order to reduce stroke-related disability and proper cardiovascular risk factor management is important for reducing the burden of readmission after stroke.

We showed that mortality and the rates and causes of readmission differed among stroke subtypes. The risk of 30-day readmission was highest in patients with LAA and SOE subtype, likely caused by an increased vulnerability of early recurrent stroke and stroke-related events. CE subtype was associated with the poorest long-term prognosis, with both the highest risk of readmission and death within five years. Stroke subtype may provide information that can be useful in a clinical setting for attention towards new diseases and readmission after discharge from the stroke units.

We showed that readmission within 30 days after discharge was an independent risk factor for one-year mortality, and more than doubled the risk of dying within one year after ischemic stroke or TIA. Readmissions might thus have a mediating effect on stroke survival due to interference with functional recovery and poorer prognosis associated with the diseases causing readmission after stroke.

Appendix

1. The modified Rankin Scale (mRS)
2. Trial of ORG 10172 Acute Stroke Treatment (TOAST)

Rankin Scale (mRS) Dag 7 (eller tidligere hvis avreise <7 døgn)

Ja ☐ Nei ☐ Dato ☐☐.☐☐.☐☐ Score: ☐

Score	
0	**Ingen symptomer og ingen begrensninger i dagliglivet**
1	**Lette symptomer, men i stand til å utføre alle vanlige aktiviteter** *"Er det problemer med å lese/skrive, snakke eller finne riktige ord, problemer med balanse, synsproblemer, nummenhet, svakhet, vanskeligheter med å svelge, eller andre symptomer som følge av slaget?"*
2	**Begrensninger i sosiale aktiviteter, men uavhengig i ADL** *"Er det blitt en endring i arbeidsevne eller evne til å ta seg av andre?"* *"Er det blitt en endring i evne til å delta i tidligere sosiale aktiviteter eller fritidsaktiviteter?"* *"Har han/hun problemer i samvær eller er blitt isolert?"*
3	**Har behov for noe hjelp (instrumental ADL), men kan gå uten hjelp** *"Er det nødvendig med hjelp til å lage et enkelt måltid, gjøre husarbeid, passe på penger, gjøre innkjøp eller reise med buss, bil nær hjemmet?"*
4	**Kan ikke gå uten hjelp, trenger hjelp i daglige aktiviteter (basic ADL), men trenger ikke kontinuerlig oppfølging og hjelp** *"Er det nødvendig med hjelp til spising, daglig hygiene, bruk av toalettet, eller å gå?"*
5	**Sengeliggende, inkontinent, avhengig av kontinuerlig hjelp** *"Trenger pasienten kontinuerlig pleie og omsorg?"*
6	**Død**

TOAST klassifikasjon

☐ **Aterosklerose (sannsynlig)**
- Ingen / eller medium risiko kardial embolikilde (sykehistorie eller undersøkelser)
- Angiografi forenlig med diagnosen, eller Duplex halskar forenlig med diagnosen

☐ **Aterosklerose (mulig)**
- Ingen høy risiko kardial embolikilde (sykehistorie eller undersøkelser)
- Angiografi eller Duplex halskar ikke utført eller Duplex halskar forenlig med diagnosen, men angiografi inkonsistent

☐ **Kardial emboli (sannsynlig)**
- Høy eller medium risiko kardial embolikilde (sykehistorie eller undersøkelser)
- Medium risiko pasienter: Ingen annen årsak
- Angiografi forenlig med diagnosen, eller Duplex halskar forenlig med diagnosen

☐ **Kardial emboli (mulig)**
- Høy eller medium risiko for kardial embolikilde (sykehistorie eller undersøkelser)
- Medium risiko pasienter: Ingen annen årsak
- Angiografi ikke utført, eller Duplex halskar forenlig med diagnosen, men angiografi inkonsistent

☐ **Småkarsykdom (sannsynlig)**
- Ingen høy/medium risiko for kardial embolikilde Ingen andre årsaker funnet
- Angiografi forenlig med diagnosen, eller Duplex halskar forenlig med diagnosen

☐ **Småkarsykdom (mulig)**
- Ingen høy risiko for kardial embolikilde
- Ingen andre årsaker funnet.
- Angiografi og Duplex halskar ikke utført eller Duplex halskar forenlig med diagnosen, men angiografi inkonsistent

☐ **Annen årsak (sannsynlig)**
- Fullstendig utredning forenlig med årsaken
- Aterosklerose eller kardial emboli utelukket

☐ **Annen årsak (mulig)**
- Undersøkelser (ikke fullstendige) forenlige med annen årsak

☐ **Ukjent årsak**
- Ingen mulig årsak
- To eller flere årsaker hvor ingen peker seg ut som mer sannsynlig

Klinikk
- Klinikk må være forenlig med subtype
- TIA i samme gebet taler for aterosklerose
- TIA i annet gebet taler for kardial emboli
- Angina pectoris eller perifer karsykdom taler for aterosklerose
- Systemiske embolier taler for kardial emboli
- Hypertensjon/diabetes støtter småkarsykdom

Høy risiko kardial embolikilde
- Mekanisk ventil
- Atrieflimmer
- Sick Sinus Syndrom
- Akutt hjerteinfarkt < 4 uker
- Venstre ventrikkeltrombe
- Dilatert kardiomyopati
- akinetisk venstre ventrikkelsegment
- Venstre atriumtrombe
- Atriemyxom
- Endokarditt

Medium risiko kardial embolikilde
- Hjerteinfarkt > 4 uker, men <6 måneder
- Hjertesvikt
- Hypokinetisk venstre ventrikkelsegment
- Atrieflutter
- Biologisk ventil
- Mitralklaffprolaps
- Atrieseptumdefekt (ASD)
- Patent foramen ovale (PFO)
- Interatrialt septumaneurysme

Cerebral CT / MR (kan være negativ)
- skal ved småkarsykdom vise et lakunært infarkt < 1,5 cm sentralt i hemisfæren eller i hjernestammen
- skal ved aterosklerose eller kardial emboli vise infarkt kortikalt og/eller subkortikalt i hemisfæren eller infarkt tilsvarende en sirkumferensarterie i hjernestammen eller cerebellum
- Ved andre subtype: lingen spesifikke krav

Angiografi og Duplex ultralyd
- skal ved aterosklerose vise en stenose ≥ 50% eller ulcerasjon ≥ 2 mm i relevant arterie

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Errata

Page 6 Missing word: “start expressing” – corrected to “start by expressing”

Page 23 Wrong word: “discovering of swallowing problems” – corrected to “detection of swallowing problems”

Page 25 Wrong word and comma: “due to incomplete treatment and unresolved problems” – corrected to “caused by incomplete treatment, unresolved problems”

Page 29 Missing word and comma: “or decrease in the level of consciousness and can be” – corrected to “or a decrease in the level of consciousness, and can be”

Page 29 Wrong word: “consist risk factors” – corrected to “consistent risk factors”

Page 31 Removed word: “health clinical process of care” – corrected to “clinical process of care”

Page 37 Wrong word: “June 2007” – corrected to “July 2007”

Page 39 Wrong year: “July 2013” – corrected to “July 2007”

Page 50 Wrong word: “stroke recurrence risk of 3%” – corrected to “stroke recurrence risk was 3%”

Page 56 Wrong word: “the cause in most pneumonia” – corrected to “the cause of most pneumonia”

Page 65 Wrong word: “patients that were not readmission” – corrected to “patients that were not readmitted”

Page 70 Deleted word: “As hospitals often rely” – corrected to “Hospitals often rely”

Page 71 Wrong word: “initiative measures” – corrected to “initiate measures”

Page 72 Missing word: “Western Norway Health Authorities” – corrected to “Western Norway Regional Health Authorities”

Paper III: Table 2, “mRS score at discharge, N (%) 0-2 and 3-5” should say “mRS score at discharge, N (%) 0-1 and 2-5”

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Research Article

The Impact of Ischaemic Stroke Subtype on 30-day Hospital Readmissions

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Background. Stroke aetiology may affect the risk and causes of readmission after ischaemic stroke (IS) and transient ischaemic attack (TIA) due to differences in risk factors, functional outcome, and treatment. We aimed to examine frequencies, causes, and risk of 30-day readmission by stroke subtype, determine predictors of 30-day readmission, and study the impact of 30-day readmissions on one-year mortality. *Methods*. All surviving patients admitted with IS or TIA from July 2007 to December 2013 were followed by review of medical records for all unplanned readmissions within 30 days after discharge. Stroke subtype was classified as large-artery atherosclerosis (LAA), cardioembolism (CE), small vessel occlusion (SVO), stroke of other determined aetiology (SOE), or stroke of undetermined aetiology (SUE). Cox regression analyses were performed to assess the risk of 30-day readmission for the stroke subtypes and identify predictors of 30-day readmission, and its impact on one-year mortality. *Results*. Of 1874 patients, 200 (10.7%) were readmitted within 30 days [LAA 42/244 (17.2%), CE 75/605 (12.4%), SVO 12/205 (5.9%), SOE 6/32 (18.8%), SUE 65/788 (8.3%)]. The most frequent causes of readmissions were stroke-related event, infection, recurrent stroke/ TIA, and cardiac disease. After adjusting for age, sex, functional outcome, length of stay, and the risk factor burden, patients with LAA and SOE subtype had significantly higher risks of readmission for any cause, recurrent stroke or TIA, and stroke-related events. Predictors of 30-day readmission were higher age, peripheral arterial disease, enteral feeding, and LAA subtype. Thirty-day readmission was an independent predictor of one-year mortality. *Conclusions*. Patients with LAA or SOE have a high risk of 30-day readmission, possibly caused by an increased risk of recurrent stroke and stroke-related events. Awareness of the risk of readmission for different causes and appropriate handling according to stroke subtype may be useful for preventing some readmissions after stroke.

1. Introduction

Stroke treatment has improved considerably over the last decades, but 30-day readmission rates after stroke have remained unchanged in Norway [1]. Thirty-day readmission rates range from 6.0% to 15.0%, with infections, recurrent stroke, and cardiac conditions as leading causes [1–8]. Reducing 30-day readmission is an important target in reducing post-stroke morbidity, mortality, and health care costs [9]. Many studies have attempted to identify predictors of readmission after stroke as this might help detect high-risk patients, but results across studies are inconsistent [2]. Factors previously associated with 30-day readmission include higher age, functional status, prior stroke or cardiac disease, longer hospitalisation, and complications during stroke admission [2–4].

Aetiologies causing ischaemic stroke (IS) and transient ischaemic attack (TIA) are categorised into different stroke subtypes [10]. Cardiovascular risk factors, neurological deficits, functional outcome, and early recurrence differ between the subtypes [11–13]; therefore, stroke subtype may influence the rates and causes of 30-day readmission. In

lack of existing prediction models on the risk of 30-day readmission after stroke, estimating the risk of readmission for the different stroke subtypes might be a valuable approach for detecting patients at higher risk of readmission. This would also be easily accessible in a clinical setting. However, the impact of stroke subtype on 30-day readmission risk is not clear.

The aims of our study were to examine (1) frequency, causes, and risk of 30-day readmission for the stroke subtypes, (2) factors associated with unplanned readmission within 30 days, and (3) the impact of 30-day readmission on one-year mortality.

2. Methods

All patients with IS or TIA admitted to the Stroke Unit at the Department of Neurology, Haukeland University Hospital, from July 2007 to December 2013, were prospectively registered in the Bergen NORSTROKE Registry. The Stroke Unit serves a well-defined geographical area with approximately 275,000 inhabitants. Patients with residence outside the geographic area of the hospital at the time of index hospitalisation were excluded from the study to ensure complete follow-up after discharge.

IS was defined as an episode of neurologic deficit lasting >24 hours because of ischaemic lesions or transient ischaemic attacks where computed tomography or magnetic resonance imaging showed infarctions related to the clinical findings [14]. TIA was a clinical diagnosis defined as transient focal cerebral dysfunction lasting < 24 hours with no objective evidence of brain infarction on imaging. Electrocardiogram, echocardiography, and duplex ultrasound of the carotid arteries were obtained during hospital admission. Stroke aetiology was classified by a stroke neurologist (HN) according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria as large-artery atherosclerosis (LAA), cardioembolism (CE), small vessel occlusion (SVO), stroke of other determined aetiology (SOE), or stroke of undetermined aetiology (SUE) [10]. The National Institutes of Health Stroke Scale (NIHSS) was used to assess stroke severity on admission and day 7, or at discharge if earlier. Short-term functional outcome was determined by modified Rankin Scale (mRS) and Barthel Index (BI) on day 7 or at discharge if earlier. Clinical characteristics, treatment, medical history, comorbidity, complications, and the discharge destination were registered before discharge from the Stroke Unit. The number of traditional cardiovascular risk factors was defined as the risk factor burden (0, 1, 2, or ≥ 3). These included hypertension, diabetes mellitus, smoking, angina pectoris, peripheral arterial disease, and prior myocardial infarction. Secondary prevention from the day of discharge was based on the Norwegian guidelines for stroke treatment [15].

Two clinicians (ATB & ANK) collected information on readmission and death by reviewing electronic medical records from all ten hospitals within the region of the Western Norway Regional Health Authorities. Readmission was defined as an unplanned admission to any department at any of the hospitals within the region of the Western Norway Regional Health Authorities. All unplanned readmissions within 30 days after discharge were registered and divided into predefined categories (any cause, recurrent stroke, stroke-related event, seizure, infection, cardiac disease, fracture, venous thromboembolism, gastrointestinal haemorrhage, and other cause). Only the first readmission within each category was registered for each patient. Patients who died during index hospitalisation and patients discharged to palliative care were excluded from the analyses.

The study was approved by the Western Regional Ethics Committee, and written informed consent was obtained from all patients or their legal guardian.

Statistical analyses were performed using Stata 14.0 (Stata Corporation, College Station, TX, USA). Baseline characteristics were assessed by chi-squared test, Student's t-test, Mann–Whitney's U-test, or Kruskal-Wallis H-test as appropriate. The risks of readmission for any cause and for the most common categories of readmission were assessed by Cox regression analyses for each subtype compared to patients with other stroke subtypes. In addition to the stroke subtype, all analyses included age, sex, mRS score, length of stay, and the risk factor burden to adjust for potential confounding factors. Predictors of the 30-day readmission were assessed by Cox regression with stepwise backward elimination of all significant parameters ($P<.05$) from the univariate analyses. Age, sex, mRS score, and length of stay were forced into the multivariate analyses to adjust for potential confounding factors. The impact of 30-day readmission on one-year mortality was studied by Cox regression analyses adjusted for age, sex, mRS score, and risk factors for cerebrovascular disease and death, after excluding patients who died within 30 days after discharge.

3. Results

A total of 1989 patients were admitted to the stroke unit and diagnosed with IS (89.6%) or TIA (10.4%), of whom 101 (5.1%) died in the stroke unit, and 14 (0.7%) were discharged to palliative care. The final study population consisted of 1874 patients, of whom 200 (10.7%) were readmitted within 30 days (10.9% of IS patients, 9.2% of TIA patients, p = 0.475). The distribution of readmissions among the stroke subtypes was as follows: LAA 42/244 (17.2%), CE 75/605 (12.4%), SVO 12/205 (5.9%), SOE 6/32 (18.8%), and SUE 65/788 (8.3%). Nineteen patients had two unplanned readmissions within 30 days, and two patients had three unplanned readmissions within 30 days. Median time to first unplanned readmission was 11 days (IQR 5-19).

Baseline characteristics of the study population by 30-day readmission status are presented in Table 1. Patients who were readmitted within 30 days were in general older, had a poorer short-term functional outcome (higher mRS score and lower BI score), and a higher NIHSS score at discharge than patients not readmitted within 30 days. Readmitted patients also had more cardiovascular comorbidity and a higher risk factor burden, and more frequently experienced complications during the index hospitalisation than patients not readmitted within 30 days. Patients with LAA subtype were more likely to be readmitted, whereas patients with SVO or SUE subtype were less likely to be readmitted.

Table 1: Baseline Characteristics of the Study Population Stratified by 30-day Readmission.

	Readmitted N = 200	Not readmitted N = 1674	P
Age (years), mean ± SD	77.2 ± 11.8	72.8 ± 13.7	<0.001
Male sex	105 (52.5)	931 (55.6)	0.402
Stroke severity and functional outcome			
mRS score at discharge, median (IQR)	2 (1, 4)	2 (1, 3)	<0.001
NIHSS score at discharge, median (IQR)	3 (1, 8)	1 (0, 4)	<0.001
BI score at discharge, median (IQR)	90 (40, 100)	100 (75, 100)	<0.001
Stroke subtype			
Atherosclerosis	42 (21.0)	202 (12.1)	<0.001
Cardioembolism	75 (37.5)	530 (31.7)	0.095
Small vessel occlusion	12 (6.0)	193 (11.5)	0.018
Other determined aetiology	6 (3.0)	26 (1.6)	0.136
Undetermined aetiology	65 (32.5)	723 (43.2)	0.004
Comorbidities			
Prior stroke	49 (24.5)	324 (19.4)	0.085
Peripheral arterial disease	26 (13.0)	110 (6.6)	0.001
Diabetes	39 (19.5)	244 (14.6)	0.066
Angina pectoris	40 (20.0)	220 (13.1)	0.008
Myocardial infarction	35 (17.5)	235 (14.0)	0.188
Hypertension	133 (66.5)	922 (55.1)	0.002
Atrial fibrillation	70 (35.0)	475 (28.4)	0.051
Prior/current smoking	122 (61.0)	965 (57.7)	0.364
Risk factor burden			0.007
0	44 (22.0)	463 (27.7)	
1	66 (33.0)	643 (38.4)	
2	53 (26.5)	377 (22.5)	
≥3	37 (18.5)	191 (11.4)	
Treatment			
Intravenous thrombolysis	33 (16.5)	274 (16.4)	0.962
Thrombectomy	6 (3.0)	22 (1.3)	0.063
Complications during the stroke hospitalisation			
Urinary tract infection	38 (19.0)	187 (11.2)	0.001
Incontinence	31 (15.5)	211 (12.6)	0.248
Urinary retention	55 (27.5)	325 (19.4)	0.007
Pneumonia	24 (12.0)	105 (6.3)	0.002
Enteral feeding	29 (14.5)	106 (6.3)	<0.001
Seizures	9 (4.5)	36 (2.2)	0.040
Stroke in progression	23 (11.5)	147 (8.8)	0.206
Any complication	100 (50.0)	637 (38.1)	0.001
Length of stay, median (IQR)	6 (3, 11)	6 (3, 10)	0.553
Discharged destination			
Home	77 (38.5)	928 (56.0)	<0.001
Home nursing	28 (14.0)	166 (10.0)	0.081
Rehabilitation department	10 (5.0)	141 (8.5)	0.087
Nursing home	69 (34.5)	376 (22.7)	<0.001
Other department	16 (8.0)	47 (2.8)	<0.001

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

Table 2: Causes of unplanned readmissions within 30 days after IS or TIA by stroke subtype.

Cause of readmission	All Stroke n=1874	LAA n=244	CE n=605	SVO n=205	SOE n=32	SUE n=788	P
Any cause	**200 (10.7)**	**42 (17.2)**	**75 (12.4)**	**12 (5.9)**	**6 (18.8)**	**65 (8.3)**	**<0.001**
Recurrent stroke	**34 (1.8)**	**11 (4.5)**	**8 (1.3)**	**1 (0.5)**	**3 (9.4)**	**11 (1.4)**	**<0.001**
IS	26 (1.4)	6 (2.5)	7 (1.2)	1 (0.5)	3 (9.4)	9 (1.1)	0.001
TIA	4 (0.2)	4 (1.6)	0	0	0	0	<0.001
ICH	4 (0.2)	1 (0.4)	1 (0.2)	0	0	2 (0.3)	0.898
Stroke-related event	**51 (2.7)**	**16 (6.6)**	**11 (1.8)**	**4 (2.0)**	**3 (9.4)**	**17 (2.2)**	**<0.001**
Seizures	**5 (0.3)**	**0**	**3 (0.5)**	**0**	**0**	**2 (0.3)**	**0.647**
Infections	**37 (2.0)**	**7 (2.9)**	**13 (2.2)**	**4 (2.0)**	**0**	**13 (1.7)**	**0.703**
Pneumonia	19 (1.0)	3 (1.2)	6 (1.0)	3 (1.5)	0	7 (0.9)	0.913
UTI	9 (0.5)	1 (0.4)	4 (0.7)	0	0	4 (0.5)	0.810
Sepsis	5 (0.3)	2 (0.8)	1 (0.2)	1 (0.5)	0	1 (0.1)	0.395
Other	4 (0.2)	1 (0.4)	2 (0.3)	0	0	1 (0.1)	0.806
Cardiac disease	**26 (1.4)**	**1 (0.4)**	**17 (2.8)**	**0**	**0**	**8 (1.0)**	**0.005**
MI	6 (0.3)	0	1 (0.2)	0	0	5 (0.6)	0.350
Arrhythmias	5 (0.3)	1 (0.4)	4 (0.7)	0	0	0	0.167
Other	16 (0.9)	0	13 (2.2)	0	0	3 (0.4)	0.001
Fractures	**7 (0.4)**	**0**	**5 (0.8)**	**0**	**0**	**2 (0.3)**	**0.244**
VT	**3 (0.2)**	**1 (0.4)**	**1 (0.2)**	**0**	**0**	**1 (0.1)**	**0.846**
GI bleeding	**4 (0.2)**	**0**	**2 (0.3)**	**1 (0.5)**	**0**	**1 (0.1)**	**0.739**
Other causes	**49 (2.6)**	**13 (5.3)**	**20 (3.3)**	**3 (1.5)**	**0**	**13 (1.7)**	**0.011**

IS: ischaemic stroke, TIA: transient ischaemic attack, LAA: large artery atherosclerosis, CE: cardioembolism, SVO: small vessel occlusion, SOE: stroke of other determined aetiology, SUE: stroke of undetermined aetiology, ICH: intracerebral haemorrhage, UTI: urinary tract infection, MI: myocardial infarction, VT: venous thromboembolism, GI: gastrointestinal.
Data are presented as n (%). Only the first readmission within each category is counted.

Table 3: Age, sex, modified Rankin Scale score, length of stay and risk factor burden by stroke subtype.

	LAA N=244	CE N=605	SVO N=205	SOE N=32	SUE N=788	P
Age (years), median (IQR)	75 (66, 82)	79 (68, 86)	69 (60, 80)	47 (38, 56)	74 (64, 83)	<0.001
Male sex, N (%)	159 (65.2)	318 (52.6)	123 (60.0)	21 (65.6)	415 (52.7)	0.002
mRS score, median (IQR)	2 (0, 3)	2 (1, 4)	2 (1, 3)	1 (0, 2)	1 (0, 3)	<0.001
Length of stay (days)	5 (3, 9)	6 (3, 10)	6 (3, 10)	8 (5, 12)	6 (3, 9)	0.029
Risk factor burden, N (%)						<0.001
0	34 (13.9)	168 (27.8)	55 (26.8)	15 (46.9)	235 (29.8)	
1	83 (34.0)	234 (38.7)	86 (42.0)	17 (53.1)	289 (36.7)	
2	70 (28.7)	142 (23.5)	42 (20.5)	0 (0.0)	176 (22.3)	
≥3	57 (23.4)	61 (10.1)	22 (10.7)	0 (0.0)	88 (11.2)	

IQR: interquartile range, mRS: modified Rankin Scale.

The most frequent cause of readmission was stroke-related events: 10 with evolving strokes (NIHSS score worsening ≤ 4 points from NIHSS score at discharge with symptoms from the same vascular territory as the index stroke), 19 with aggravation of existing neurological deficits (neurological symptoms not measurable by the NIHSS score), 2 with haemorrhagic transformation, 3 with neurological complications after carotid endarterectomy, 1 with extracranial haemorrhage, 1 with carotid dissection, and 15 with other neurological symptoms. The length of index hospitalisation was slightly shorter for patients that were readmitted with a stroke-related event compared to patients that were not readmitted with a stroke-related event (median 5 days (IQR 5-8) versus median 6 days (IQR 3-10), p=0.193). Infection was the second most frequent cause of readmission, followed by recurrent stroke or TIA, and cardiac disease. The causes of readmission were unevenly distributed among the stroke subtypes (Table 2).

Table 3 shows the distribution of age, sex, mRS score, length of stay, and the risk factor burden among the stroke

Table 4: Factors Associated with 30-day Unplanned Readmission after IS or TIA.

	Hazard Ratio	95% Confidence Interval	P
Age (years)	1.020	1.006 – 1.034	0.004
Sex (male)	0.936	0.690 – 1.268	0.667
mRS score	0.990	0.894 – 1.095	0.842
Length of stay (days)	0.997	0.973 – 1.022	0.846
Peripheral arterial disease	1.577	1.007 – 2.468	0.047
LAA subtype	1.735	1.201 – 2.505	0.003
Enteral feeding	1.861	1.112 – 3.114	0.018

IS: ischaemic stroke, TIA: transient ischaemic attack, mRS: modified Rankin Scale, LAA: large artery atherosclerosis.

subtypes. After adjusting for these factors, patients with stroke due to LAA had an increased risk of readmission for any cause (HR=1.76, 95% CI 1.22-2.53, p=0.002), readmission with recurrent stroke or TIA (HR = 3.31, 95% CI 1.55-7.07, p=0.002), and readmission with stroke-related events (HR=2.98, 95% CI 1.55-5.74, p=0.001). Patients with SOE had an increased risk of readmission for any cause (HR=2.81, 95% CI 1.11-7.10, p=0.029), recurrent stroke (HR=6.00, 95% CI 1.26-28.57, p=0.024), and stroke-related events (HR=4.27, 95% CI 1.19-15.35, p=0.026). The recurrent strokes in the SOE group were ascribed to dissection of the middle cerebral artery, giant cerebral aneurysm, and pancreatic cancer, respectively. Patients with SUE had a lower risk of readmission for any cause compared to other subtypes (HR=0.71, 95% CI 0.52-0.97, p=0.031). Patients with CE subtype had an increased risk of readmission due to cardiac disease (HR=2.56, 95% CI 1.07-6.09, p=0.034). Exclusion of SOE from the regression models did not alter any findings.

Factors independently associated with 30-day readmission from the final Cox regression model were increasing age, history of peripheral arterial disease, enteral feeding during index hospitalisation (nasogastric tube or percutaneous endoscopic gastrostomy), and LAA subtype (Table 4).

Within 30 days, 61 (3.3%) patients died, of whom 29 (47.5%) had been readmitted. There were no significant differences in 30-day mortality between stroke subtypes (LAA 3.3%, CE 4.1%, SVO 1%, SOE 0%, and SUE 3.3%, p = 0.203). Within one year, 139 (7.4%) additional patients died, of whom 36 (25.9%) had been readmitted within 30 days. One-year mortality significantly differed between the stroke subtypes (LAA 11.8%, CE 14.0%, SVO 3.4%, SOE 3.1%, and SUE 10.2%, p = 0.001). Thirty-day readmission significantly increased the risk of one-year mortality in patients surviving 30 days after discharge after adjusting for age, sex, mRS score, and risk factors for cerebrovascular disease and death (HR 2.57, 95% CI 1.75 – 3.78, p < 0.001).

4. Discussion

This is one of the first and the current largest studies investigating the impact of stroke subtype on 30-day readmission after ischaemic stroke or TIA. Our study demonstrates that 30-day readmission varies depending on the stroke subtype, ranging from 5.9% for patients with SVO to 17.2% for patients with LAA and 18.8% for patients with SOE. A study performed in a younger stroke population found that 14% of patients with thrombotic strokes were readmitted within 30 days, whereas 22% of patients with CE strokes were readmitted within 30 days [16]. Another study found that 22% of patients with CE and 20% of patients with LAA subtype were readmitted within 30 days, whereas SUE had the lowest rate of readmission, with 8% readmitted within 30 days [4]. These discrepancies are likely due to study populations with different demography, lower mean ages, and different distribution of stroke subtypes than ours.

The varying readmission rates between the stroke subtypes could be caused by differences in age, functional outcome, and risk factors. After adjusting for these factors, patients with SVO, which had the lowest number of readmission, did not have a lower risk of readmission compared to other subtypes. However, the risk of 30-day readmission was significantly increased in patients with LAA and SOE subtype, whereas patients with SUE had a significantly lower risk of readmission after adjusting for confounders.

Two of the most common causes of readmission were stroke-related events and recurrent stroke. The risk of recurrent stroke is highest in the early phase after the initial IS or TIA [11]. Awareness and attention towards recurrent strokes and a low threshold for readmission in cases which could represent recurrent strokes, may contribute to a high rate of readmissions with stroke-related events such as aggravation or fluctuation of existing neurologic symptoms. Thus, education of patients and their families in the natural course of the post-stroke period may reduce some of these readmissions.

In concordance with recent studies on 30-day recurrence, only 1.8 % were readmitted with a recurrent stroke within 30 days [17, 18]. However, 4.5% of patients with LAA subtype were readmitted with recurrent stroke within 30 days. LAA subtype has previously been associated with early recurrent stroke [11, 12]. This could be caused by repetitive shedding of thrombi from unstable atherosclerotic plaques triggered by shear stress [19], or cerebral ischaemia induced by carotid surgery in some patients, but the reason for the high risk of early recurrence in patients with LAA is not yet fully understood. Patients with LAA or SOE subtype had increased risks of recurrent stroke and stroke-related events, which likely explains their overall increased risk of 30-day readmission. LAA subtype was also an independent predictor of 30-day readmission, probably due to increased recurrence of recurrent stroke or TIA and aggravation of neurological symptoms. Few studies have reported stroke recurrence for patients with SOE as a result of low numbers of subjects. The increased risk of recurrence as well as readmission for any cause and stroke-related events for patients with SOE in our study could be a chance finding due to a low number of subjects and should be interpreted with caution. However, it is possible that SOE includes some rare aetiologies with an especially high risk of early recurrence.

Infection was a frequent complication during index hospitalisation in our study, and the second most common cause of readmission. Early infections after stroke are associated with enteral feeding which might explain why enteral feeding independently increased the risk of 30-day readmission [20]. Poor functional outcome has also been associated with post-stroke infections [21]. Even though there were differences in short-term functional outcome between the stroke subtypes, the median mRS score was 2 or less for all stroke subtypes. This might explain why we found no differences in infection-related readmission between the stroke subtypes. Poor functional outcome and length of stay have been associated with early readmission [2, 3]. This could be due to an increased risk of infection in patients with poor functional outcome as well as a higher risk of undetected medical complications if patients are discharged too early [21]. The present study unexpectedly found that poor functional outcome and length of stay were not associated with readmission. This could be due to higher rates of cardiovascular and stroke-related readmissions than infections, which, in contrast to infections, likely are not affected by functional outcome or length of stay to the same extent. This might also explain why we found no differences in readmission between IS and TIA patients.

Thirty-day readmission was significantly associated with an increased risk of one-year mortality. This has previously been demonstrated [9] and could perhaps be due to interference with functional recovery after stroke if the patient is readmitted. Also, the cause of readmission might contribute to a worse prognosis and higher post-stroke mortality, as demonstrated for post-stroke pneumonia and recurrent stroke [22, 23]. Even though most readmissions are unavoidable when reviewed retrospectively [24], a reduction in readmission rates have been demonstrated with early outpatient visits by physicians, and with education of patients about relevant diagnoses, and confirmation of the medication plan [25–27]. Sufficient monitoring and care for prevention of medical complications, both during hospitalisation and in the immediate post-hospital care setting, may be key factors in preventing some readmissions. In addition, a thorough evaluation for detecting the underlying cause of the stroke and awareness of readmission risk and treatment according to the stroke subtype may be useful in preventing some readmissions after stroke.

A weakness of the present study is the lack of information in the few cases where patients were transferred to other hospital departments. It is unlikely that we have missed some readmissions, as we exclusively included patients served by our hospital and obtained data on readmissions from all ten hospitals in our region. Our study is unable to demonstrate a direct, causative relationship between stroke subtype and readmissions as it was an observational study. The study-design limits the generalisability due to possible selection bias, but it provides precise and verified clinical data with the use of a comprehensive registry and medical record review, contributing to a better understanding of underlying causes of the readmissions.

5. Conclusions

Readmission within 30 days after IS and TIA remains frequent in Norway. The risk and causes of 30-day readmission differed between the stroke subtypes and were especially high in patients with LAA and SOE. Stroke subtype may substitute as a 30-day readmission risk estimator in lack of more precise risk-estimation models, but more studies are needed to confirm our findings.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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II

Causes and Predictors for Hospital Readmission after Ischemic Stroke

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Background: Readmission after stroke is frequent, but limited data are available in Europe. This study aimed at assessing frequencies, causes, and factors associated with early and late unplanned readmissions within 1 year after discharge from ischemic stroke hospitalization. *Methods:* All surviving ischemic stroke patients admitted to the Department of Neurology, Haukeland University Hospital, Norway, between July 1, 2007, and June 30, 2012, were followed from discharge until August 1, 2012. Information on readmissions was collected by medical chart reviews. Logistic regression was performed to assess factors associated with early (≤90 days) and late (91-365 days) readmission. *Results:* Of 1175 patients discharged alive, 18.8% were readmitted within 90 days, and 24.5% were readmitted between day 91 and 365. Most frequent causes were infections, recurrent ischemic stroke, other cardiovascular events, and events related to index stroke. Early readmission was associated with older age, impaired physical function, atherosclerotic etiology of index stroke, and a higher risk factor burden. Late readmission was associated with older age and prior myocardial infarction. Early readmitted patients had shorter length of index admission, poorer physical function and higher frequencies of atherosclerotic etiology of index stroke, atrial fibrillation, and complications with infection during the index admission compared to patients readmitted late. *Conclusions:* Readmission after ischemic stroke is frequent, especially in the early period after discharge. Diagnoses and predictors varied according to time point for readmission, reflecting different underlying mechanisms for causes of readmission. Causes of early readmission may include a prothrombotic state and disposition for recurrent infections. **Key Words:** Readmission—rehospitalization—stroke—ischemic stroke—outcome research.

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Conditions leading to readmission of stroke survivors cause greater disability for the patient, increased mortality, and higher costs for the society.[1,2] However, limited data are available regarding the burden on readmission after stroke, especially in Europe.

Within 1 year after discharge, 31%-49% of stroke survivors experience readmissions,[3-6] and nearly half of the first readmissions occur within 90 days.[6] Leading causes of readmission are infections, recurrent cerebrovascular events, and other cardiovascular diseases.[5-7]

Predictors of readmission after stroke might help prevent some of the complications and readmissions. Previously reported factors associated with readmission have been older age, impaired physical function,[6,8-10]

increased length of index admission for stroke,[3,6,10] complication during index admission,[6,11] and comorbidities such as diabetes mellitus, prior stroke, coronary artery disease, and atrial fibrillation.[6] Despite many attempts, there are no standardized models for predicting risk of readmission after stroke.[12]

The aims of this hospital-based cohort study were to (1) estimate frequencies of unplanned readmissions after discharge from ischemic stroke hospitalization, (2) determine the causes for readmission, and (3) investigate factors associated with readmission.

We hypothesized that the risk of readmission was high during the first 90 days after discharge, because some patients may be in a prothrombotic state, experience delayed hospital-acquired infections, or be prone to infections after ischemic stroke. We therefore investigated early (≤90 days) and late (91-365 days) readmissions separately.

Materials and Methods

All patients with acute ischemic stroke admitted to the Department of Neurology at Haukeland University Hospital between July 1, 2007, and June 30, 2012, were prospectively registered in the Bergen NORSTROKE Registry. The stroke unit serves a well-defined region of approximately 250,000 people. We obtained written informed consent from all patients. This study includes patients living in the local area of Haukeland University Hospital. Patients who died during index admission were excluded from the study.

Ischemic stroke was defined as a neurologic deficit lasting more than 24 hours or a clinically transient ischemic attack where computed tomography or magnetic resonance imaging showed infarctions related to the initial clinical symptoms.[13] The National Institutes of Health Stroke Scale (NIHSS) score was used to assess stroke severity on admission and day 7. Short-term outcome was determined by modified Rankin Scale (mRS) and Barthel Index on day 7 (or at discharge if discharged earlier than 7 days). Electrocardiogram and duplex ultrasound of the carotid arteries were obtained. Stroke etiology was classified by the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[14] Clinical characteristics, medical history, and stroke cause were registered by a neurologist within 1 day after admission. The risk factor burden was defined by traditional risk factors as 0, 1, 2, and 3 or more risk factors. These included hypertension, diabetes mellitus, smoking, angina pectoris, peripheral vascular disease, and prior myocardial infarction. Other risk factors registered were prior cerebrovascular disease, atrial fibrillation, and prior coronary intervention. Complications during the index admission included urinary incontinence, urinary retention, urinary tract infection (UTI), pneumonia, seizures, and stroke in progression (NIHSS score worsening ≥4 points during the first week after stroke onset compared to NIHSS score on admission). Secondary preventive treatment on discharge was based on the Norwegian guidelines for stroke treatment.[15]

Information regarding hospital readmissions after discharge from the index stroke until August 1, 2012, was collected by medical chart reviews. Outcome was defined as the first unplanned readmission. Subjects were dichotomized during follow-up as readmitted or not readmitted. When investigating frequencies, causes, and predictors of readmission, readmitted patients were divided into 2 groups: readmission ≤ 90 days (early readmission) and readmission 91-365 days (late readmission). Patients who could not be followed for the respective time intervals, and patients who were either dead or had been readmitted before the 91-365 days interval, were excluded from the respective intervals. Possible hospital-acquired infections were assessed by comparing the proportion of readmission with infections the first 30 days after discharge to day 31-60. A possible prothrombotic state was assessed by comparing the proportion of readmissions with recurrent ischemic stroke or myocardial infarction ≤ 90 to day 91-180.

The study was approved by the Western Regional Ethics Committee (REC).

Statistics

Proportions were used to describe frequencies and causes of readmission. Student *t* test, chi-square test, and Mann–Whitney *U* test were used to investigate baseline characteristics. Logistic regression analyses were performed to identify factors independently associated with early and late readmission. Analyses were performed by stepwise backward elimination where first step included all parameters that turned out significant ($P < .05$) in the univariate analyses. Age, sex, and mRS were forced into each regression to adjust for potentially confounding factors. Kaplan–Meier was performed to illustrate readmission and survival based on etiology. Statistical analyses were performed with Stata 12.0 (Stata Corporation, College Station, TX, USA).

Results

A total of 1250 patients were admitted with acute ischemic stroke between July 1, 2007, and June 30, 2012. During the index admission, 75 (6.0%) patients died. Thus, 1175 patients were discharged alive and included in the study.

Frequencies and Causes of First Unplanned Readmission

Frequencies and causes of first unplanned readmission are presented in Table 1. Of all patients who could be followed for 1 year after discharge (n = 943), 355 (37.7%) had

Table 1. *Causes of first unplanned readmission*

Readmission cause	Early readmission ≤90 days n (%)	Late readmission 91-365 days n (%)
Cardiovascular disease	28 (2.4)	19 (2.5)
Myocardial infarction	9 (.8)	6 (.8)
Angina	4 (.3)	3 (.4)
Other heart disease	15 (1.3)	10 (1.3)
DVT/pulmonary embolism	2 (.2)	1 (.1)
Cerebrovascular disease	28 (2.4)	29 (3.9)
Ischemic stroke	25 (2.2)	24 (3.2)
Hemorrhagic stroke	1 (.1)	2 (.3)
TIA	2 (.2)	3 (.4)
Events related to index stroke*	34 (2.9)	20 (2.7)
Seizure	8 (.7)	6 (.8)
Fracture	11 (.9)	13 (1.7)
Hip fracture	7 (.6)	5 (.7)
Other fracture	4 (.3)	8 (1.1)
Infection	36 (3.1)	38 (5.1)
Pneumonia	21 (1.8)	14 (1.9)
Urinary tract infection	7 (.6)	7 (.9)
Other infection	8 (.7)	17 (2.3)
Ulcers/GIT bleeding	9 (.8)	3 (.4)
Warfarin complication	3 (.3)	1 (.1)
Other causes	59 (5.1)	53 (7.1)
Readmitted patients, total	218 (18.8)	183 (24.5)
All patients	1162 (100)	747 (100)

Abbreviations: DVT, deep vein thrombosis; GIT, gastrointestinal; TIA, transient ischemic attack.

*Question of stroke, stroke in progression, extracerebral hemorrhage.

at least 1 unplanned readmission during the first year. Most frequent causes for readmission were infections, recurrent ischemic stroke, other cardiovascular diseases, and events related to index stroke (stroke in progression, subarachnoid hemorrhage, subdural hemorrhage, and readmissions with presumed recurrent stroke where this was disproved).

More patients were readmitted with recurrent ischemic stroke or acute myocardial infarction ≤90 days (n = 34) than during day 91-180 (n = 12) after discharge (P = .02). Patients with pneumonia during index admission had significantly higher frequencies of readmission with pneumonia both ≤90 days and 91-365 days. The associations were also significant when adjusting for age, sex, and the severity of the stroke (≤90 days: odds ratio [OR] = 7.0, P < .001; 91-365 days: OR = 5.2, P = .015). Patients with UTI during index admission had higher frequencies of readmission for UTI both ≤90 days and 91-365 days (both P < .01). Patients with urinary retention during index admission had higher frequencies of readmission with UTI ≤90 days (P < .01). When adjusting for age, sex, and the severity of the stroke, readmission with UTI ≤90 days was significantly associated with UTI (OR = 5.8, P = .031) or urinary retention (OR = 10.2, P = .041) during index admission. More patients were readmitted with infections the first 30 days (n = 22) compared to day 31-60 (n = 6) after discharge (P = .01).

Factors Associated with First Unplanned Readmission

Early Readmission (≤90 days)

Baseline characteristics of patients readmitted early are presented in Table 2. More patients discharged to home nursing or nursing homes were readmitted early compared to patients discharged home (n = 115 [27%] versus n = 71 [12%], P < .001). Patients readmitted early had higher frequencies of atherosclerotic etiology of index stroke (n = 37 [17%], P ≤ .001) and cardioembolic stroke (n = 90 [42%] P = .023), and lower frequencies of stroke due to small-vessel disease (n = 14 [7%], P = .003). As to the locations of index ischemic stroke, only watershed infarct was associated with early readmission (n = 14 [44%], P < .001). Nine (60%) of these patients were readmitted with recurrent ischemic stroke or events related to the index stroke. Early readmission was not associated with length of index admission. Logistic regression showed an association between early readmission and older age, higher mRS score, atherosclerotic etiology of index stroke, atrial fibrillation, and the risk factor burden (Table 3).

Late Readmission (91-365 days)

Baseline characteristics of patients readmitted late are presented in Table 2. Patients readmitted late were more often discharged to home nursing or nursing homes compared to discharged home (n = 69 [30%] versus n = 83 [20%], P = .005). Logistic regression showed an association between late readmission, higher age, and prior myocardial infarction, and an inverse association with small-vessel disease stroke. Higher mRS score was not associated with late readmission (Table 4).

Early versus Late Readmitted Patients

Logistic regression with early versus late readmission as dependent variable showed that early readmitted patients had higher mRS score, shorter length of index admission, and higher frequencies of atherosclerotic etiology of index stroke, atrial fibrillation, and complications with pneumonia or UTI than patients who were readmitted late (Table 5). Figure 1 illustrates readmission over time grouped by the TOAST classification.

Discussion

This is the first study to investigate the burden of readmission after ischemic stroke in Norway. More

Table 2. *Baseline characteristics of patients readmitted early (≤90 days) and late (91-365 days)*

	Early readmission ≤90 days			Late readmission 91-365 days		
Chararteristics	Readmitted	Not readmitted	*P*	Readmitted	Not readmitted	*P*
Total	218 (18.8)	944 (81.2)		183 (24.5)	564 (75.5)	
Males	112 (51.4)	517 (54.8)	.37	106 (57.9)	308 (54.6)	.43
Age (y) mean ± SD	77.2 ± 11.5	72.4 ± 13.7	<.01	75.1 ± 12.5	71.1 ± 13.8	<.01
mRS score, median (IQR)	3 (1, 4)	2 (1, 3)	<.01	2 (1, 4)	2 (1, 3)	.03
NIHSS score, median (IQR)	4 (2, 9)	3 (1, 6)	<.01	4 (1, 7)	3 (1, 6)	.04
BI score, median (IQR)	90 (45, 100)	100 (70, 100)	<.01	100 (65, 100)	100 (80, 100)	.01
Prior comorbidity						
Cerebrovascular disease	53 (24.9)	176 (18.9)	.05	46 (25.1)	104 (18.5)	.05
Peripheral vascular disease	23 (10.6)	62 (6.6)	.04	16 (8.7)	38 (6.7)	.36
Diabetes	42 (19.4)	131 (14.0)	.04	32 (17.6)	73 (13.0)	.12
Angina pectoris	44 (20.3)	119 (12.6)	<.01	29 (15.9)	62 (11.0)	.08
Myocardial infarction	40 (18.4)	129 (13.7)	.08	36 (19.7)	58 (10.3)	<.01
Coronary intervention	27 (12.5)	119 (12.6)	.95	30 (16.5)	55 (9.8)	.01
Hypertension	141 (64.7)	512 (54.2)	<.01	107 (58.5)	294 (52.1)	.14
Atrial fibrillation	93 (42.7)	274 (29.0)	<.01	61 (33.3)	145 (25.7)	.045
Prior/current smoking	42 (30.9)	218 (42.0)	.02	30 (29.1)	141 (45.6)	<.01
Risk factor burden			<.01			.07
0	37 (17.7)	224 (24.8)		45 (25.6)	142 (26.1)	
1	68 (32.5)	374 (41.5)		62 (35.2)	236 (43.5)	
2	71 (34.0)	197 (21.8)		39 (22.2)	107 (19.7)	
≥3	33 (15.8)	107 (11.9)		30 (17.0)	58 (10.7)	
IS etiology			<.01			.08
Atherosclerosis	37 (17.1)	98 (10.4)		18 (9.9)	62 (11.0)	
Cardioembolism	90 (41.5)	313 (33.3)		69 (38.1)	170 (30.2)	
Small-vessel disease	14 (6.4)	129 (13.7)		16 (8.8)	90 (16.0)	
Other determined	5 (2.3)	12 (1.3)		1 (.6)	7 (1.2)	
Undetermined	71 (32.7)	389 (41.4)		77 (42.5)	234 (41.6)	
Complications						
Urinary tract infection	46 (21.1)	121 (12.8)	<.01	22 (12.0)	68 (12.1)	.99
Incontinence	45 (20.6)	148 (15.7)	.08	38 (20.8)	70 (12.4)	<.01
Urinary retention	72 (33.0)	231 (24.5)	<.01	54 (29.5)	125 (22.2)	.04
Pneumonia	30 (13.8)	72 (7.6)	<.01	12 (6.6)	30 (5.3)	.53
Seizures	9 (4.1)	22 (2.3)	.14	5 (2.7)	14 (2.5)	.85
Stroke in progression	34 (21.7)	98 (14.3)	.02	18 (14.4)	58 (14.0)	.91
Length of index admission, median (IQR)	7 (4, 12)	7 (4, 11)	.46	7 (4, 12)	7 (4, 11)	.17
Discharged to			<.01			<.01
Home	71 (32.6)	504 (53.4)		83 (45.4)	331 (58.7)	
Home nursing	43 (19.7)	113 (12.0)		30 (16.4)	58 (10.3)	
Rehabilitation	15 (6.9)	87 (9.2)		16 (8.7)	55 (9.8)	
Nursing home	72 (33.0)	201 (21.3)		39 (21.3)	105 (18.6)	
Other department	17 (7.8)	39 (4.1)		15 (8.2)	15 (2.7)	

Abbreviations: BI, Barthel Index; IQR, interquartile range; IS, ischemic stroke; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation.

Data are expressed as n (%) unless specified.

than one-third of our patients experienced at least 1 unplanned readmission within a year after discharge. This is comparable to studies from other countries where 1-year readmission varied from 37% to 40%.[5,10,16] A hospital-based study from Taiwan reported a lower 1-year readmission frequency of 31%,[6] which may be because of lower mean age than in our study. Nearly half of all unplanned readmissions in the present study occurred within 90 days after discharge, which has also been reported previously.[6,7]

Infection was the most common cause of readmission. When investigating this further, we found that pneumonia, UTIs, or urinary retention during the index admission was associated with readmission because of

Table 3. *Factors associated with early readmission (≤ 90 days)*

Characteristics	Odds ratio	95% Confidence interval	*P*
Age (y)	1.02	1.00-1.03	.02
Sex	1.12	.81-1.55	.50
mRS score*	1.21	1.09-1.35	<.01
Atherosclerosis†	1.85	1.17-2.92	<.01
Number of risk factors	1.28	1.08-1.51	<.01
Atrial fibrillation	1.54	1.08-2.19	.02

Abbreviation: mRS, modified Rankin Scale.
*Per mRS point.
†Ischemic stroke etiology based on TOAST.

pneumonia or UTIs respectively. An explanation may be that some patients are prone to recurrent infections even when treated adequately, because of repeated pulmonary aspirations or urinary retention and urinary catheterization. Another explanation why infections were frequent may be that the immunological state is impaired after a stroke, thus increasing the risk of infections in the early phase after discharge.[17] A significantly higher proportion of patients were readmitted with infections during the first 30 days compared to day 31-60, and it is possible that early readmissions for infection might also relate to delayed hospital-acquired infections or insufficiently treated hospital infections. Alertness for subclinical infections during the hospital stay and appropriate rehabilitation such as early supported discharge may reduce readmission for infection.[18]

Vascular events were a frequent cause of readmission, especially within 90 days after discharge. This has previously been reported[6] and could be caused by a prothrombotic state in some patients in the early phase after ischemic stroke. Atherosclerotic etiology and atrial fibrillation were associated with early readmission. A high risk of early stroke recurrence has been reported for atherosclerotic infarctions.[19] We found that patients readmitted early had higher frequencies of complications with infection during index admission compared to patients readmitted late. In addition, infection is becoming well recognized as a risk factor for cardiovascular events. The mechanisms are thought to be a prothrombotic state caused by atherosclerotic plaque instability, immunohematological alterations, activation of platelets and proinflammatory cytokines, and endothelial dysfunction.[20] Keeping in mind that recurrent ischemic stroke was a common cause of early readmission, this suggests that preventing infections could be important when aiming to prevent readmission.

In addition to causing stroke by thromboembolic mechanisms, atherosclerosis may cause hemodynamic stroke. Watershed infarctions are often caused by hemodynamic compromise due to severe arterial stenosis.[21] In our study, patients with watershed infarctions had especially high frequencies of readmission for recurrent ischemic stroke

Table 4. *Factors associated with late readmission (91-365 days)*

Characteristics	Odds ratio	95% Confidence interval	*P*
Age (y)	1.02	1.00-1.03	<.01
Sex	.79	.55-1.14	.21
mRS score *	1.11	.98-1.25	.10
Small-vessel disease†	.56	.31-.98	.04
Prior myocardial infarction	1.89	1.18-3.04	<.01

Abbreviation: mRS, modified Rankin Scale.
*Per mRS point.
†Ischemic stroke etiology based on TOAST.

Table 5. *Factors associated with early (≤ 90 days) versus late (91-365 days) readmission*

Characteristics	Odds ratio	95% Confidence interval	*P*
Age (y)	1.00	.98-1.02	.73
Sex	1.29	.84-1.99	.25
mRS score*	1.21	1.01-1.45	.035
Pneumonia†	3.08	1.36-6.98	<.01
Urinary tract infection†	1.96	1.04-3.69	.04
Atrial fibrillation	1.65	1.04-2.61	.035
Length of index admission	.95	.92-.98	<.01
Atherosclerosis‡	2.63	1.38-5.02	<.01

Abbreviation: mRS, modified Rankin Scale.
*Per mRS point.
†Complication during index admission.
‡Ischemic stroke etiology based on TOAST.

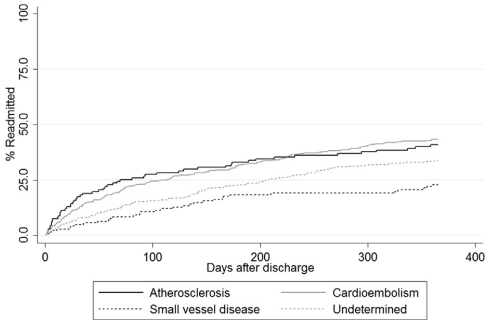

Figure 1. *Kaplan–Meier failure estimates on readmission by etiology of index ischemic stroke (TOAST).*

within 90 days. It is likely that both hemodynamic compromise and a prothrombotic state contribute to high readmission frequencies for vascular events in patients with atherosclerotic ischemic stroke. We suggest that thorough investigation to disclose the etiology of stroke during the hospital stay may result in better secondary preventive treatment and thereby reduce readmission because of recurrent stroke.

Patients with ischemic stroke due to small-vessel disease had significantly lower frequencies of both early and late readmission (Fig 1). The low readmission risk was also present when adjusting for physical function. It is possible that small-vessel disease is less associated with factors causing readmission than other etiologies for ischemic stroke. Furthermore, small-vessel disease does not cause cortical lesions with deficits such as neglect, apraxia, and cognitive impairment, which might lead to readmission.

Impaired physical function was associated with early readmission. An association between impaired physical function and 1-year readmission has previously been reported.[6,10] Impaired physical function is associated with both infection and vascular events. Our study suggests that the association between impaired physical function and readmission is especially high in the early period after discharge because of infection and ischemic stroke. Adequate physical exercise after discharge might improve this.

We found that the risk factor burden was associated with early readmission. We have not been able to identify any other comparable studies which have made such a score in connection with readmission after stroke. Our findings add new information on the importance of the risk factor burden. Other studies have shown that the risk factor burden is associated with mortality and vascular events.[22,23]

Increased length of index admission for stroke may be associated with readmission.[6,8,9] We found, however, no difference in length of index admission between the readmitted and not readmitted patients. Furthermore, the median length of index admission in our population was substantially lower than previously reported by other studies[7,8] and comparable to only 2 other studies which both reported length of index admission to be associated with readmission.[6,9] However, comparing early and late readmission showed that patients who were readmitted early had shorter length of index admission than patients readmitted late, even when adjusting for confounding factors including physical function and infection during index admission. This may indicate that some patients with stroke-related infections were discharged too early.

To our knowledge, this is the first study comparing patients readmitted within different time intervals during the first year after ischemic stroke. A weakness of our study is that there is no assessment of treatments the patients may have received after discharge or of compliance. All information and subjects are collected from a single hospital, and caution is needed when generalizing our findings. Furthermore, a few patients may have been readmitted to other hospitals although our hospital is responsible for all unplanned readmissions of the patients in this study.

In conclusion, readmission is frequent, especially in the early period after hospital discharge. Diagnoses and predictors varied according to time point for readmission, reflecting different underlying mechanisms for causes of readmission. Causes of early readmission may include a prothrombotic state and disposition for recurrent infections.

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III

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RESEARCH ARTICLE Open Access

One-year versus five-year hospital readmission after ischemic stroke and TIA

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Abstract

Background: The burden of hospital readmission after stroke is substantial, but little knowledge exists on factors associated with long-term readmission after stroke. In a cohort comprising patients with ischemic stroke and transient ischemic attack (TIA), we examined and compared factors associated with readmission within 1 year and first readmission during year 2–5.

Methods: Patients with ischemic stroke or TIA who were discharged alive between July 2007 and October 2012, were followed for 5 years by review of medical charts. The timing and primary cause of the first unplanned readmission were registered. Cox regression was used to identify independent risk factors for readmission within 1 year and first readmission during year 2–5 after discharge.

Results: The cohort included 1453 patients, of whom 568 (39.1%) were readmitted within 1 year. Of the 830 patients that were alive and without readmission 1 year after discharge, 439 (52.9%) were readmitted within 5 years. Patients readmitted within 1 year were older, had more severe strokes, poorer functional outcome, and a higher occurrence of complications during index admission than patients readmitted during year 2–5. Cardiovascular comorbidity and secondary preventive treatment did not differ between the two groups of readmitted patients. Higher age, poorer functional outcome, coronary artery disease and hypertension were independently associated with readmission within both 1 year and during year 2–5. Peripheral artery disease was independently associated with readmission within 1 year, and atrial fibrillation was associated with readmission during year 2–5.

Conclusions: More than half of all patients who survived the first year after stroke without any readmissions were readmitted within 5 years. Patients readmitted within 1 year and between years 2–5 shared many risk factors for readmission, but they differed in age, functional outcome and occurrence of complications during the index admission.

Keywords: Hospital readmission, Ischemic stroke, TIA, Risk factors, Epidemiology, Outcome

Background

Stroke survivors carry a high risk of new diseases due to functional disability, neurological deficits and pre-existing cardiovascular risk factors and comorbidity [1]. Readmissions after stroke are frequent, particularly during the first 3 months after stroke when more than half of all patients readmitted within 1 year presents [2–4]. The neurological and functional impairments often improve during the first year after stroke, but the number of readmitted patients steadily increases in the chronic phase, and between 67 and 83% of all stroke patients have been readmitted within 5 years [4–6]. Despite this, less is known about the long-term risk of readmission for stroke patients who survive the early phase after stroke without any readmissions.

Several studies have examined predictors for readmission after stroke. Data on causes of readmissions after stroke can be used to prevent future avoidable readmissions. Although the study findings are inconsistent, factors associated with 1-year readmission include older age [2, 7–10], a history of stroke [2], diabetes mellitus, [11] coronary artery disease [2], in-hospital complications [2, 10], longer length of hospital stay [2, 7, 11], and poor functional outcome [2,

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11]. Predictors of readmission in the chronic phase of stroke after 1 year have not been identified. Furthermore, it is possible that patients readmitted within the first year differ from patients that experience the first readmission later, as the early readmission may to a higher extent be directly related to acute post-stroke complications and the post-acute stroke treatment, and patients readmitted within the first year may be more severely impaired than patients readmitted later.

The aims of our study were to identify 1) predictors of readmission within 1 year, 2) predictors of first readmission during year 2–5, and 3) factors differing between patients readmitted within 1 year and patients with the first readmission during year 2–5 after ischemic stroke and transient ischemic attack (TIA). We hypothesized that patients readmitted within the first year are more affected by acute complications during the index admission, have more severe strokes and poorer functional outcome than patients readmitted later, and that traditional cardiovascular risk factors are more prominent in patients readmitted within the first year after stroke.

Methods

All patients > 18 years of age admitted to the Stroke Unit at the Department of Neurology with ischemic stroke or TIA, Haukeland University Hospital from July 1, 2007 to September 31, 2012, were prospectively registered in the Bergen NORSTROKE Registry. The Stroke Unit serves a well-defined geographical area with approximately 275,000 inhabitants. For the present study, we excluded all patients with residence outside the hospital catchment area due to difficulties of long-term follow-up. We also excluded patients who died during the index admission and patients who were discharged to palliative care.

Ischemic stroke was defined as an episode of neurologic deficit lasting > 24 h or clinical symptoms of TIA where computed tomography or magnetic resonance imaging showed acute infarctions related to the initial symptoms [12]. TIA was diagnosed clinically and was defined as transient focal cerebral dysfunction < 24 h with no objective evidence of acute brain infarction on imaging. Duplex ultrasound of the carotid arteries, echocardiogram, Holter monitoring, echocardiography and serology were obtained during hospital admission. Stroke etiology was classified by an experienced stroke neurologist (HN) according to the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) criteria [13]. Stroke severity was determined by the National Institutes of Health Stroke Scale (NIHSS) score on admission and day 7, or at discharge if earlier. Short-term functional outcome was determined by modified Rankin Scale (mRS) and Barthel Index on day 7 or at discharge if earlier. Clinical characteristics, treatment, comorbidity, medical history, in-hospital complications and discharge destination were registered. Secondary prevention was based on the Norwegian guidelines for stroke treatment [14].

Information on readmission and death within 5 years after discharge was collected by review of the medical records from all nine hospitals in the region of the Western Norway Regional Health Authorities. Readmission was defined as the first unplanned admission for any cause to any hospital department after the index admission. The timing and primary cause of the first readmission were registered, and readmitted patients were divided into two groups: first readmission within 1 year after discharge, and first readmission within year 2–5. Causes of readmission were categorized as recurrent stroke, stroke-related event (including neurological deterioration, hemorrhagic transformation of cerebral infarction, neurological complications after carotid endarterectomy, and suspected stroke or TIA with no specific final diagnosis), seizure, cardiac disease, infection, fracture, gastrointestinal hemorrhage, venous thromboembolism, and other cause. Hemorrhagic transformation was defined as petechial or confluent hemorrhage in the same area as the primary infarction.

The study was approved by the Regional Ethics Committee for Medical and Health Research Ethics in Western Norway (REC West). Written informed consent was obtained from all patients. In cases where patients suffered severe strokes and were not able to give informed consent, this was obtained from their legally authorized representatives as required by the Regional Ethics Committee for Medical and Health Research Ethics in Western Norway.

Statistics

Baseline characteristics were examined by using the χ^2 test for categorical variables and Student's *t*-test or Mann-Whitney's *U*-test for the continuous variables as appropriate. A Kaplan-Meier failure curve was made to demonstrate the incidence of readmission over time, and the log-rank test was used to compare the incidence of readmission between ischemic stroke and TIA. Cox regression analyses were used to examine factors associated with readmission within 1 year and first readmission during year 2–5 after discharge with backward selection method. Patients who were readmitted or dead within 1 year after discharge were excluded from the analyses on readmission from year 2–5. Patients who died or moved outside the area of the Western Norway Regional Health Authorities before the end of follow-up without any readmission were censored in the Kaplan-Meier analysis and the Cox regression models. All multivariate analyses were performed with stepwise backward elimination starting with all significant parameters from the univariate analyses ($P < .05$). Age, sex and

mRS score were forced into each analysis to adjust for potential confounding. Statistical analyses were performed using Stata 14.0 (Stata Corporation, College Station, TX, USA).

Results

The study cohort included 1453 patients discharged alive from our stroke unit, of whom 1303 (89.7%) were diagnosed with ischemic stroke and 150 (10.3%) were diagnosed with TIA. Baseline characteristics of the study cohort are shown in Table 1.

Within 1 year after discharge from the index admission, 568 (39.1%) patients were readmitted and 163 (11.2%) patients were dead, of whom 108 (66.3%) had been readmitted at least once. Of the 830 patients that were alive and free of readmission 1 year after discharge, 439 (52.9%) were readmitted within 5 years. Figure 1 demonstrates the incidence estimates of readmission over time. There were no differences in the 5-year incidence of readmission between ischemic stroke and TIA. After 5 years, a total of 1007 patients (69.3%) had been readmitted, and 358 patients (24.6%) were alive and without any readmission. A total of 492 patients (33.9%) were dead wihtin 5 years after discharge, of whom 280 (56.9%) had been readmitted within 1 year and 124 (25.2%) had the first readmission during year 2–5.

Baseline characteristics of patients readmitted within 1 year and patients with the first readmission between year 2–5 are shown in Table 2. On univariate analysis, patients readmitted within 1 year were older, had a poorer short-term functional outcome, a higher discharge NIHSS score, and more complications during index admission than patients with the first readmission between year 2–5. A stroke subtype of small vessel occlusion was more frequent in patients with the first readmission between year 2–5. Cardiovascular risk factors and comorbidity did not differ between the two groups of readmitted patients, and neither did prescribed secondary preventive treatment at discharge or at the time of the first readmission. A higher percentage of patients readmitted within the first year had stopped smoking before the index admission, whereas more patients had quit smoking after the index admission in patients that were readmitted between years 2–5. Of the patients that were smoking at the time of the index stroke, 37% of the patients readmitted between year 2–5 had stopped smoking compared to 28% of patients readmitted during the first year ($p = 0.144$). Patients readmitted within 1 year were more often discharged to nursing homes and less often discharged home without help than patients readmitted between year 2–5.

Increasing age, poorer short-term functional outcome (increasing mRS score), and a history of peripheral artery disease, coronary artery disease, or hypertension, independently increased the risk of readmission within 1 year after discharge, whereas a stroke subtype of small vessel occlusion significantly decreased the risk of

Table 1 Baseline characteristics of the study cohort

Characteristics	Values
Age (years), mean ± SD	73.1 ± 13.7
Male sex, N (%)	782 (53.8)
NIHSS score at discharge, median (IQR)	1 (0, 4)
mRS score at discharge, median (IQR)	2 (1, 3)
Barthel Index at discharge, median (IQR)	100 (70, 100)
Stroke subtype, N (%)	
Large-artery atherosclerosis	193 (13.3)
Cardioembolism	473 (32.6)
Small vessel occlusion	159 (10.9)
Other determined etiology	20 (1.4)
Undetermined etiology	608 (41.8)
Comorbidity, N (%)	
Prior stroke	299 (20.6)
Peripheral artery disease	102 (7.0)
Coronary artery disease	325 (22.4)
Diabetes mellitus	211 (14.5)
Atrial fibrillation	428 (29.5)
Hypertension	813 (56.0)
Ever-smoker	832 (57.3)
Complications during index admission, N (%)	
Pneumonia	112 (7.7)
Enteral feeding	117 (8.1)
Urinary tract infection	184 (12.7)
Urinary retention	327 (22.5)
Urinary incontinence	212 (14.6)
Seizures	35 (2.4)
Stroke in progression	130 (9.0)
Any complication	599 (41.2)
Length of stay, median (IQR)	6 (3, 11)
Treatment at discharge, N (%)	
Antiplatelet	917 (63.1)
Anticoagulation	465 (32.0)
Antihypertensive	1021 (70.3)
Statins	1023 (70.4)
Discharge status, N (%)	
Home without care	792 (54.6)
Home with care	164 (11.3)
Rehabilitation department	112 (7.7)
Nursing home	337 (23.2)
Other department	46 (3.2)

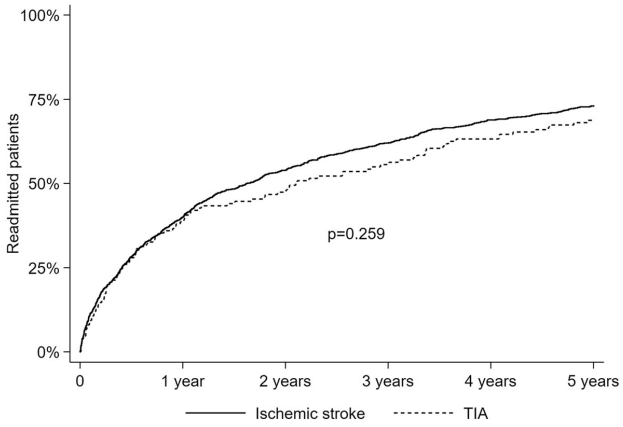

Fig. 1 Kaplan Meier failure curves showing incidence estimates of readmission within 5 years for patients with ischemic stroke ($n = 1303$) or TIA ($n = 150$)

readmission within 1 year (Table 3). Increasing age, poorer short-term functional outcome, a history of coronary artery disease, atrial fibrillation, or hypertension, independently increased the risk of readmission between year 2–5 if alive and free of readmission 1 year after discharge (Table 4).

The most frequent cause of the first readmission within 1 year was infection, followed by recurrent stroke, stroke-related event and cardiac disease In contrast, cardiac disease was the most frequent cause of the first readmission for patients readmitted during years 2–5, followed by infection, stroke-related event and recurrent stroke (Table 5).

Discussion

We found that 69.3% were readmitted within 5 years after ischemic stroke or TIA, with more than half of all readmitted patients presenting during the first year. A smaller Norwegian study demonstrated that 56% of all readmissions within 10 years presented during the first year after stroke and similar patterns have been reported from the US [4–6]. In line with previously reported 1-year readmission rates between 31 and 55%, we found that 39% were readmitted within the first year after discharge [2, 3, 6, 15, 16]. The high rates of readmission during the first year after stroke might reflect an increased vulnerability for post-stroke complications such as infections, recurrent stroke and other cardiovascular events in the early phase after stroke [1].

We also found that more than half of all patients that survived for 1 year without any readmission were readmitted within 5 years. The frequency of the different causes of readmission varied slightly depending on the timing of the first readmission, but infection, cardiac disease, recurrent stroke and stroke-related events were the four most common causes in both time periods. Higher age, poor functional outcome, hypertension and coronary artery disease were all independently associated with readmission both within 1 year and during year 2–5. This indicates that even if the patients survive the vulnerable early period after stroke, they still have a high risk of readmission for the same causes as patients readmitted during the first year after stroke, and the same factors might impact the risk of readmission also in the more chronic phase after stroke.

Higher age and poorer short-term functional outcome predicted readmission within 1 year and from year 2-5, but patients readmitted within 1 year were older, had a poorer short-term functional outcome and more complications during index admission than patients readmitted later. Complications during the index stroke admission have been associated with early readmission in several studies, and probably relates to both high age and poor functional outcome [17, 18]. Higher age and poor functional outcome have been identified as predictors for readmission after stroke in several other studies [2, 7–11]. Although age is a non-modifiable risk factor for readmission, a focus on improving and maintaining physical function and mobility during the stroke hospitalization and in the period after discharge for patients at all ages is important and could potentially help prevent some readmissions.

Hypertension and coronary artery disease were identified as common predictors of readmission within 1 year and from year 2-5, and contrary to our hypothesis, the vascular risk factor profile was not more prominent in patients readmitted within 1 year. Hypertension and coronary artery disease are important risk factors for

Table 2 Distribution of baseline characteristics between patients readmitted within 1 year and patients with the first readmission between year 2–5

	≤1 year *N* = 568	Year 2–5 *N* = 439	*P*
Age (years), mean ± SD	76.2 ± 12.5	73.3 ± 13.1	< 0.001
Male sex, N (%)	298 (52.5)	242 (55.1)	0.401
NIHSS score at discharge, median (IQR)	2 (0, 5)	1 (0, 3)	< 0.001
mRS score at discharge, N (%)			< 0.001
0–2	323 (56.9)	304 (69.3)	
3–5	245 (43.1)	135 (30.8)	
Barthel Index at discharge, median (IQR)	100 (60, 100)	100 (85, 100)	< 0.001
Stroke diagnosis, N (%)			0.992
Ischemic stroke	510 (89.8)	395 (90.0)	
TIA	58 (10.2)	44 (10.0)	
Stroke subtype, N (%)			0.070
Large-artery atherosclerosis	85 (15.0)	53 (12.1)	
Cardioembolism	206 (36.3)	152 (34.6)	
Small vessel occlusion	44 (7.8)	55 (12.5)	
Other determined etiology	8 (1.4)	3 (0.7)	
Undetermined etiology	225 (39.6)	176 (40.1)	
Comorbidity, N (%)			
Prior stroke	137 (24.1)	96 (21.9)	0.401
Peripheral artery disease	54 (9.5)	29 (6.6)	0.097
Coronary artery disease	162 (28.5)	103 (23.5)	0.071
Diabetes mellitus	97 (17.1)	64 (14.6)	0.283
Atrial fibrillation	197 (34.7)	135 (30.8)	0.188
Hypertension	358 (63.0)	256 (58.3)	0.128
Ever-smoker	384 (67.6)	285 (64.9)	0.371
Complications during index admission, N (%)			
Pneumonia	54 (9.5)	22 (5.0)	0.007
Enteral feeding	59 (10.4)	24 (5.5)	0.005
Urinary tract infection	86 (15.1)	49 (11.2)	0.066
Urinary retention	154 (27.1)	76 (17.3)	< 0.001
Urinary incontinence	107 (18.8)	47 (10.7)	< 0.001
Seizures	17 (3.0)	9 (2.1)	0.350
Stroke in progression	59 (10.4)	25 (5.7)	0.008
Any complication	281 (49.5)	157 (35.8)	< 0.001
Length of stay, median (IQR)	6 (3, 11)	6 (3, 10)	0.190
Discharge status, N (%)			< 0.001
Home without care	257 (45.4)	255 (58.1)	
Home with care	84 (14.8)	57 (13.0)	
Rehabilitation department	37 (6.5)	35 (8.0)	
Nursing home	162 (28.6)	83 (18.9)	
Other department	26 (4.6)	9 (2.1)	
Treatment at discharge, N (%)			
Platelet inhibitor	379 (66.7)	302 (68.8)	0.487
Anticoagulation	203 (35.7)	148 (33.7)	0.805

Table 2 Distribution of baseline characteristics between patients readmitted within 1 year and patients with the first readmission between year 2–5 *(Continued)*

	≤1 year N = 568	Year 2–5 N = 439	P
Antihypertensive drug	363 (63.9)	285 (64.9)	0.740
Statins	390 (68.7)	322 (73.4)	0.105
Treatment at readmission, N (%)			
Platelet inhibitor	368 (64.8)	281 (64.0)	0.798
Anticoagulation	211 (37.2)	151 (34.4)	0.367
Antihypertensive drug	371 (65.3)	286 (65.2)	0.956
Statins	365 (64.3)	267 (60.8)	0.263
Smoking status at readmission, N (%)			0.036
Stopped smoking before index stroke	242 (66.1)	160 (58.0)	
Stopped smoking after index stroke	35 (9.6)	43 (15.6)	
Still smoking at readmission	89 (24.3)	73 (26.5)	

recurrent stroke and cardiac disease, which were frequent causes of readmission within both 1 year and year 2-5 in our study, and are highly important causes of death after stroke [19, 20]. Hypertension is the most important modifiable risk factor for stroke and other cardiovascular diseases, and blood pressure reduction reduces the risk of recurrent stroke, myocardial infarction and cardiovascular death after stroke [21]. This emphasizes the importance of accurate and aggressive treatment of cardiovascular risk factors in preventing new vascular events and vascular mortality after ischemic stroke and TIA.

Even though cardiovascular risk factors did not differ significantly between patients readmitted within 1 year and patients readmitted during year 2–5, recurrent stroke and stroke-related events were more frequent causes of readmission within 1 year, whereas cardiac disease was a more frequent cause of readmission for patients that were readmitted during year 2–5. We have only included the cause of the first uplanned readmission in this study, but studies have shown similar results in relation to recurrent stroke and cardiac disease, with the highest incidences of recurrent stroke observed in the early period after stroke, and lower, yet more stable, yearly incidences of myocardial infarction and congestive heart failure [4, 22].

Even though they differ in functional outcome, ischemic stroke and TIA patients did not differ in the incidence of readmission. Compared to ischemic stroke patients, both lower, similar and higher rates of readmission in TIA patients have been reported [8, 23–25]. This could possibly be explained by differences in case mix and use of secondary prevention and adherence to medical treatment [25]. Nevertheless, TIA patients have the same risk factor profile and underlying causes of their ischemic event as patients with ischemic stroke, and should be provided accurate secondary treatment in order to reduce subsequent vascular events and readmissions.

Our study has some limitations. Some patients may have been readmitted to a hospital outside the region of the Western Norwegian Regional Health authorities, even though this region involves a large geographical area of Western Norway. Furthermore, we have no information on smoking status or medical treatment received after discharge in patients that were not readmitted, and no information on treatment

Table 3 Risk factors for readmission within 1 year after ischemic stroke or TIA

	Hazard Ratio	95% Confidence Interval	P
Age, years	1.02	1.01–1.03	<.001
Male sex	1.02	0.86–1.21	.835
mRS score	1.15	1.09–1.22	<.001
Small vessel occlusion	0.67	0.49–0.91	.010
Peripheral artery disease	1.42	1.06–1.89	.018
Coronary artery disease	1.29	1.07–1.57	.009
Hypertension	1.26	1.05–1.50	.012

Table 4 Risk factors for readmission between year 2-5 if alive and without readmission 1 year after ischemic stroke or TIA

	Hazard Ratio	95% Confidence Interval	P
Age, years	1.03	1.02–1.04	<.001
Male sex	1.13	0.93–1.38	.217
mRS score	1.09	1.02–1.16	.014
Coronary artery disease	1.50	1.20–1.89	<.001
Atrial fibrillation	1.25	1.01–1.55	.046
Hypertension	1.38	1.13–1.68	.001

Table 5 Primary cause of the first readmission after ischemic stroke or TIA

	≤ 1 year N = 568		Year 2–5 N = 439	
	N	%	*N*	%
Recurrent stroke	72	12.7	36	8.2
Ischemic stroke	59	10.4	25	5.7
Intracerebral hemorrhage	6	1.1	5	1.1
TIA	7	1.2	6	1.4
Stroke-related events[a]	72	12.7	45	10.3
Seizures	19	3.4	4	0.9
Heart disease	62	10.9	75	17.1
Myocardial infarction	16	2.8	23	5.2
Arrhythmias	17	3.0	22	5.0
Heart failure	13	2.3	12	2.7
Other	16	2.8	18	4.1
Infections	107	18.8	70	16.0
Pneumonia	46	8.1	25	5.7
Urinary tract infection	24	4.2	15	3.4
Sepsis	11	1.9	4	0.9
Other	26	4.6	26	5.9
Fractures	37	6.5	33	7.5
Hip fracture	19	3.3	16	3.6
Other	18	3.2	17	3.9
Gastrointestinal hemorrhage	14	2.5	6	1.4
Venous thromboembolism	4	0.7	3	0.7
Other causes	181	31.9	167	38.0

[a]Neurological deterioration, hemorrhagic transformation of cerebral infarction, neurological complications after carotid endarterectomy, and suspected stroke or TIA with no specific final diagnoses

compliance. As the study cohort originates from a single site, the generalizability of our findings may be limited. A strength of our study is the ascertainment of data related to the readmissions made by review of medical records, and the inclusion of a relatively large study population investigated in a single stroke center according to a predefined protocol with comprehensive data collection. Although other studies have reported resembling results regarding rates and causes of long-term readmission after stroke, our study elaborates on existing knowledge by describing rates, causes and predictors of readmission for patients who survive the first year after stroke without any readmission.

Conclusions

More than half of all patients who survived the first year after stroke without any readmission, were readmitted within 5 years. Patients with the first readmission during year 2–5 after discharge shared several risk factors with patients readmitted within 1 year, but they differed in relation to short-term functional outcome, age, and the frequency of complications during index admission. Our results indicate that further improvement in the effort of reducing post-stroke complications and hospital readmissions should continue beyond the acute phase after stroke. More studies are needed to establish predictors of readmission after stroke in the long-term perspective.

Abbreviations

IQR: Interquartile range; mRS: Modified Rankin scale; NIHSS: National Institute of Stroke Scale; SD: Standard deviation; TIA: Transient ischemic attack; TOAST: Trial of Org 10,172 in Acute Stroke Treatment

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Availability of data and materials

The dataset for the current study are available from the corresponding author on reasonable request.

Authors' contributions

AB and HN conceived the study. AB, AK, HN, LT and UA contributed on data collection, and AB carried out the data analysis and interpretation with input by AK, HN and NL. AB wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Ethics approval and consent to participate

The study was approved by the Regional Ethics Committee for Medical and Health Research Ethics in Western Norway (REK vest). Written informed consent was obtained from all patients. In cases where patients suffered severe strokes and were not able to give informed consent, this was obtained from their legally authorized representatives as required by the Regional Ethics Committee for Medical and Health Research Ethics in Western Norway.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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IV

Five-year Readmission and Mortality Differ by Ischemic Stroke Subtype

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Tables: 3

Figures: 3

Abstract

Background: Ischemic stroke subtype may influence the risk of readmission and mortality after ischemic stroke (IS) and transient ischemic attack (TIA) due to differences in comorbidity, risk factors, and stroke severity. We aimed to study the five-year incidence and risk of all-cause readmission, cause-specific readmission and mortality after IS or TIA by stroke subtype.

Methods: The medical records of 1453 patients admitted with IS or TIA to the stroke unit at Haukeland University Hospital, Norway, between 2007 and 2012 were reviewed for identification of unplanned readmissions within five years after discharge. Stroke etiology was classified as large-artery atherosclerosis (LAA), cardioembolism (CE), small vessel occlusion (SVO), stroke of other determined etiology (SOE), or stroke of undetermined etiology (SUE). Kaplan-Meier estimates and Cox regression analyses were used to determine incidences and risk of readmission and death.

Results: The five-year incidence of all-cause readmission was 72.6% (74% LAA, 81% CE, 65% SVO, 55% SOE, and 68% SUE), with infections, cardiac disease, stroke-related events and fractures as the most frequent causes. Compared to patients with other subtypes, SVO subtype had a 21% lower risk of all-cause readmission and a 48% lower risk of death, whereas CE had a 25% higher risk of all-cause readmission and a 34% higher risk of death. CE subtype also had a 75% higher risk of readmission due to cardiac disease, whereas the risk of readmission due to cardiac disease was 23% lower in patients SUE compared to other subtypes.

Conclusion: The five-year incidence of readmission and mortality varied among the stroke subtypes. The risk of readmission and death is especially high in patients with CE subtype, and lowest for patients with SVO subtype.

Introduction

Stroke patients are at increased risk of subsequent disease, and readmissions are common.[1, 2] The risk of readmission is particularly high in the early phase after stroke, with 30-day estimates ranging from 6% to 21%, and one-year estimates from 31% to 55%.[2-6] Most studies on long-term outcome after stroke have focused on recurrent stroke, vascular events, and mortality.[7] However, nonvascular events such as infections and fractures are also frequent in the chronic phase of stroke, and less than 15% of all stroke patients survive for more than five years without being readmitted.[2, 6, 8, 9]

Ischemic stroke and transient ischemic attack (TIA) are heterogeneous disorders caused by various pathologies including large-artery atherosclerosis, cardioembolism, small vessel occlusion and other less common causes.[10] Risk factors, treatment and outcome highly depend on stroke subtype, which further may influence the risk and the causes of readmission.[11, 12] Most studies investigating the risk of readmission after stroke have not differentiated between stroke subtypes, which might contribute with important information in the evaluation for risk of new diseases and unwanted readmissions.

The aim of this study was to investigate the five-year incidence and risk of readmission after ischemic stroke or TIA. To elucidate the underlying causes of long-term hospital readmission, the risks of all-cause readmission and cause-specific readmission were examined for each stroke subtype.

Methods

All patients >18 years of age with ischemic stroke or TIA admitted to the Stroke Unit at Haukeland University Hospital from July 2007 to October 2012, were prospectively registered in the Bergen NORSTROKE Registry. The study cohort included all patients living inside the hospital catchment area (≈ 275 000 residents). Patients with residence outside the hospital catchment area at the time of the index stroke admission were excluded to ensure complete follow-up. Patients who died during the index hospitalization or were discharged to palliative care were also excluded.

Ischemic stroke was defined as a neurologic deficit lasting >24 hours or as clinical symptoms

of transient ischemic attacks but with computed tomography or magnetic resonance imaging (MRI) evidence of acute infarction related to the initial symptoms.[13] TIA was defined as a transient episode of neurological dysfunction <24 hours with no objective evidence of acute brain infarction on imaging.[14] Electrocardiogram, duplex ultrasound of the carotid arteries, Holter monitoring, echocardiography and serology were obtained during hospital admission. Ischemic stroke etiology was classified by an experienced stroke neurologist (HN) according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria as large-artery atherosclerosis (LAA), cardioembolism (CE), small vessel occlusion (SVO), stroke of other determined etiology (SOE), or stroke of undetermined etiology (SUE).[10] The TOAST criteria were also applied for etiologic classification of TIAs, with findings of a ipsilateral significant (≥50%) atherosclerotic stenosis and no competing cause classified as LAA, findings of a cardioembolic source and no competing cause classified as CE, findings of lacunar clinic and no competing cause classified as SVO, findings of other specific etiology such as arterial dissection classified as SOE, and in cases with no identified cause, incomplete evaluation, or two or more identified possible causes as SUE. Stroke severity was determined by National Institutes of Health Stroke Scale (NIHSS) on admission and on day 7 or discharge if earlier. Short-term functional outcome was determined by modified Rankin Scale (mRS) on day 7 or discharge if earlier. Demographics, clinical characteristics, treatment, comorbidity, medical history and discharge destination were registered. Discharge date was defined as discharge from the stroke unit to home or primary care or an in-hospital transfer to another department/rehabilitation department. A variable representing the total number of traditional cardiovascular risk factors (hypertension, diabetes mellitus, smoking, angina pectoris, prior myocardial infarction and peripheral artery disease) was made and defined as the risk factor burden (0, 1, 2, and ≥3 risk factors). Secondary prevention was based on the Norwegian guidelines for stroke treatment.[15]

All patients were followed for five years after discharge by review of electronic medical records, which also includes information on mortality from the National Registry of Norway. Mortality and all unplanned readmissions to any department at the ten hospitals within the area of the Western Norway Regional Health Authorities were registered. Patients that moved outside the area of the Western Norway Regional Health Authorities during follow-up were censored at the time of change of address. The main reason for readmission was categorized as recurrent stroke, stroke-related event (neurological deterioration, hemorrhagic transformation of cerebral infarction, neurological complications after carotid endarterectomy,

suspected stroke or TIA with no specific final diagnosis), seizure, cardiac disease, infection, fracture, gastrointestinal hemorrhage, venous thromboembolism, and other cause. Only the first readmission within each category was counted for each patient.

Written informed consent to participate in the registry was obtained from all patients or their legally authorized representatives. Research related to the registry including extraction of information after discharge was approved by the Western Regional Ethics Committee.

Statistics

Baseline characteristics were assessed by chi-squared test for categorical variables and t-test, rank-sum test, ANOVA or Kruskal-Wallis test for the continuous variables. Kaplan-Meier estimates and log-rank test were used to determine and compare the incidence of all-cause readmission, cause-specific readmission, and mortality for the stroke subtypes. Kaplan Meier failure curves were made to demonstrate readmission over time by stroke subtype (SOE excluded due to low number of subjects). To evaluate for possible bias, we compared the Kaplan-Meier incidence estimates of all-cause and cause-specific readmissions to age-adjusted cumulative incidence estimates from survival models that accounted death as a competing risk (Fine-Gray model).[16] Cox regression was used to investigate the five-year risk of all-cause and cause-specific readmission for each stroke subtype (SOE excluded due to low number of subjects). Covariates included in the regression models were age, sex, mRS score and risk factor burden, which are known risk factors for readmission after stroke that differ between the stroke subtypes.[11, 17, 18] Since the mRS score was measured on day 7, we also included premorbid care-status. Statistical analyses were performed using Stata 15.0 (Stata Corporation, College Station, TX, USA).

Results

Of the 1453 patients (89.7% IS and 10.3% TIA patients), 1007 patients (69.3%) were readmitted within five years. There was a total of 3021 readmission, and the median time from discharge to the first readmission was 284 days (IQR 74, 736). Baseline characteristics of the study population stratified by readmission status after five years are shown in Table 1. Readmitted patients were older, had a poorer short-term functional (higher mRS score), more cardiovascular comorbidity, and had a higher risk factor burden.

Table 1. Baseline characteristics of the study cohort

Characteristics	Readmitted N = 1007	Not readmitted N = 446	P
Age (years), mean (SD)	74.9 (12.8)	69.2 (14.8)	<0.001
Male sex, N (%)	540 (53.6)	242 (54.3)	0.823
Admission NIHSS score, median (IQR)	3 (1, 6)	2 (1, 5)	0.039
Discharge NIHSS score, median (IQR)	1 (0, 4)	1 (0, 3)	0.085
Discharge mRS score, median (IQR)	2 (1, 3)	1 (0, 3)	0.021
Discharge diagnose, N (%)			0.714
Ischemic stroke	905 (89.9)	398 (89.2)	
TIA	102 (10.1)	48 (10.8)	
Stroke subtype, N (%)			0.001
Large artery atherosclerosis	138 (13.7)	55 (12.3)	
Cardioembolism	358 (35.6)	115 (25.8)	
Small vessel occlusion	99 (9.8)	60 (13.5)	
Other determined etiology	11 (2.0)	9 (1.1)	
Undetermined etiology	401 (39.8)	207 (46.4)	
Comorbidity, N (%)			
Prior stroke or TIA	233 (23.1)	66 (14.8)	<0.001
Prior coronary artery disease	265 (26.3)	60 (13.5)	<0.001
Prior peripheral artery disease	83 (8.2)	9 (4.3)	0.006
Atrial fibrillation	332 (33.0)	96 (21.5)	<0.001
Hypertension	614 (61.0)	199 (44.6)	<0.001
Diabetes mellitus	161 (16.0)	50 (11.2)	0.017
Prior/current smoking	583 (57.9)	249 (55.8)	0.463
Risk factor burden, N (%)			<0.001
0	231 (22.9)	162 (36.3)	
1	381 (37.8)	177 (39.7)	
2	253 (25.1)	76 (17.0)	
≥3	142 (14.1)	31 (7.0)	
Acute treatment, N (%)			
Intravenous thrombolysis	138 (13.7)	75 (16.8)	0.122
Mechanical thrombectomy	12 (1.2)	5 (1.1)	0.908
Discharge destination, N (%)			<0.001
Home	512 (51.0)	280 (62.8)	
Home nursing	141 (14.0)	23 (5.2)	
Rehabilitation department	72 (7.2)	40 (9.0)	
Nursing home	245 (24.4)	92 (20.6)	
Other department	35 (3.5)	11 (2.5)	
Premorbid care, N (%)			0.026
None	830 (83.7)	384 (86.5)	
Home nursing	141 (14.2)	44 (9.9)	
Permanently institutionalized	21 (2.1)	16 (3.6)	
Employed before stroke, N (%)	162 (16.4)	151 (34.3)	<0.001
Higher education level, N (%) †	99 (31.6)	64 (41.6)	0.034

SD indicates standard deviation; mRS, modified Rankin Scale; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack. †Missing data in 986 patients

Table 2 demonstrates the baseline characteristics of the study population stratified by stroke subtype. Stroke patients with CE had the highest admission NIHSS score, and patients with SVO had the highest discharge NIHSS score. Stroke patients with CE and SVO had the poorest short-term functional outcome. Stroke patients with LAA had the highest risk factor burden, and the highest occurrence of peripheral artery disease, hypertension and smoking.

Table 2. Baseline characteristics by stroke subtype.

Characteristics	LAA N=193	CE N=473	SVO N=159	SOE N=20	SUE N=608	P
Age (years), mean (SD)	74.3 (9.9)	75.5 (14.3)	69.2 (13.4)	45.2 (15.0)	72.9 (13.0)	<0.001
Male sex, N (%)	123 (63.7)	236 (49.9)	95 (59.8)	13 (65.0)	315 (51.8)	0.005
Discharge diagnose						<0.001
Ischemic stroke	159 (82.4)	447 (94.5)	159 (100.0)	20 (100.0)	518 (85.2)	
TIA	34 (17.6)	26 (5.5)	0 (0.0)	0 (0.0)	90 (14.8)	
Acute treatment						
Intravenous thrombolysis	39 (20.2)	74 (15.6)	8 (5.0)	3 (15.0)	89 (14.6)	0.002
Mechanical thrombectomy	2 (1.0)	11 (2.3)	0 (0.0)	0 (0.0)	4 (0.7)	0.061
Admission NIHSS score, median (IQR)	2 (0, 6)	3 (1, 8)	2 (1, 4)	1 (0, 3)	2 (1, 5)	<0.001
Discharge NIHSS score, median (IQR)	1 (0, 4)	1 (0, 5)	2 (1, 3)	0 (0, 3)	1 (0, 3)	0.036
Discharge mRS score median (IQR)	2 (0, 3)	2 (1, 4)	2 (1, 3)	1 (0, 2)	1 (0, 3)	<0.001
Comorbidity, N (%)						
Prior stroke or TIA	47 (24.4)	86 (18.2)	25 (15.7)	2 (10.0)	139 (22.9)	0.062
Coronary artery disease	55 (28.5)	120 (25.4)	22 (13.9)	1 (5.0)	127 (20.9)	0.002
Peripheral artery disease	38 (19.7)	25 (5.3)	6 (3.8)	0 (0.0)	33 (5.4)	<0.001
Atrial fibrillation	9 (4.7)	343 (72.5)	1 (0.6)	0 (0.0)	75 (12.3)	<0.001
Hypertension	124 (64.3)	288 (60.9)	81 (50.9)	3 (15.0)	317 (52.1)	<0.001
Diabetes mellitus	30 (15.5)	63 (13.3)	25 (15.7)	2 (10.0)	91 (15.0)	0.857
Prior/current smoking	138 (71.5)	229 (48.4)	96 (60.4)	11 (55.0)	358 (58.9)	<0.001
Risk factor burden, N (%)						<0.001
0	27 (14.0)	129 (27.3)	41 (25.8)	10 (50.0)	186 (30.6)	
1	70 (36.3)	183 (38.7)	72 (45.3)	10 (50.0)	223 (36.7)	
2	51 (26.4)	113 (23.9)	32 (20.1)	0 (0.0)	133 (21.9)	
≥3	45 (23.3)	48 (10.2)	14 (8.8)	0 (0.0)	66 (10.9)	
Premorbid care, N (%)						0.443
None	165 (87.3)	382 (81.6)	135 (85.4)	19 (95.0)	513 (85.4)	
Home nursing	21 (11.1)	74 (15.8)	18 (11.4)	1 (5.0)	71 (11.8)	
Permanently institutionalized	3 (1.6)	12 (2.6)	5 (3.2)	0 (0.0)	17 (2.8)	

SD, standard deviation; mRS, modified Rankin Scale; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

Kaplan-Meier incidence estimates of all-cause readmission, cause-specific readmissions and mortality for the stroke subtypes are shown in Table 3. The cumulative incidence of all-cause hospital readmission was 9.9 % at one month (95% CI 8.4-11.5), 39.9% at one year (95% CI 37.4-42.5) and 72.6% at five years (95% CI 70.2-74.9). The five-year incidence of all-cause readmission varied significantly among the stroke subtypes, from 55% for SOE and 81% for CE subtype (Figure 1). After adjusting for age, sex, mRS score, premorbid care-status and risk factor burden, the risk of all-cause readmission was 25% higher for CE (HR=1.25, 95% CI 1.09-1.43, p=0.001) and 21% lower for SVO (HR=0.79, 95% CI 0.64-0.98, p=0.033) compared to other subtypes.

Table 3. Incidence estimates of death, all-cause and cause-specific readmission within 5 years after IS or TIA

	Incidence rates %						
	Total N=1453	LAA N=193	CE N=473	SVO N=159	SOE N=20	SUE N=608	P
Death	34.5	36.3	42.8	20.1	10.0	30.4	<0.001*
All-cause readmission	72.6	73.7	81.3	65.0	55.0	68.4	<0.001*
Recurrent stroke	13.8	13.9	13.9	12.8	20.3	13.8	0.894
IS	11.3	11.0	12.0	9.4	20.3	11.2	0.639
ICH	1.3	0.5	1.6	4.0	0.0	0.6	0.017*
TIA	2.0	3.1	1.1	0.0	0.0	2.9	0.085
Stroke-related event	14.9	16.4	16.0	12.9	15.0	14.3	0.807
Seizure	4.3	4.1	6.1	1.4	5.0	3.8	0.114
Cardiac disease	20.8	19.4	29.1	15.9	10.0	17.1	<0.001*
MI	6.9	8.6	6.8	5.5	5.3	7.1	0.884
Arrhythmia	7.0	6.1	11.9	6.3	0.0	4.3	<0.001*
Heart failure	5.2	1.9	9.6	1.5	5.0	4.0	<0.001*
Other	5.9	6.5	8.4	3.5	0.0	4.9	0.087
Infection	29.7	35.4	33.6	23.4	10.3	27.6	0.005*
Pneumonia	15.0	17.7	19.7	9.6	5.0	12.8	0.008*
UTI	9.1	10.8	8.2	8.7	0.0	9.5	0.491
Sepsis	4.4	8.5	4.2	2.9	0.0	3.9	0.041*
Other	8.8	8.0	11.3	7.1	5.6	7.9	0.494
Fracture	12.3	6.5	16.6	8.8	0.0	12.4	0.004*
Hip fracture	6.6	2.1	8.9	5.5	0.0	6.9	0.032*
Other	6.6	4.5	9.4	4.7	0.0	6.2	0.117
VTE	1.6	1.9	1.3	1.4	5.3	1.5	0.740
GI hemorrhage	4.4	5.0	4.3	4.9	0.0	4.2	0.899
Other diagnosis	46.5	51.3	52.7	39.8	25.6	43.1	0.002*

IS, ischemic stroke; TIA, transient ischemic attack; LAA, large artery atherosclerosis; CE, cardioembolism; SVO, small vessel occlusion; SOE, stroke of other determined etiology; SUE, stroke of undetermined etiology; ICH, intracerebral hemorrhage; UTI, urinary tract infection; MI, myocardial infarction; VTE, venous thromboembolism; GI, gastrointestinal.

*P<0.05 after exclusion of SOE

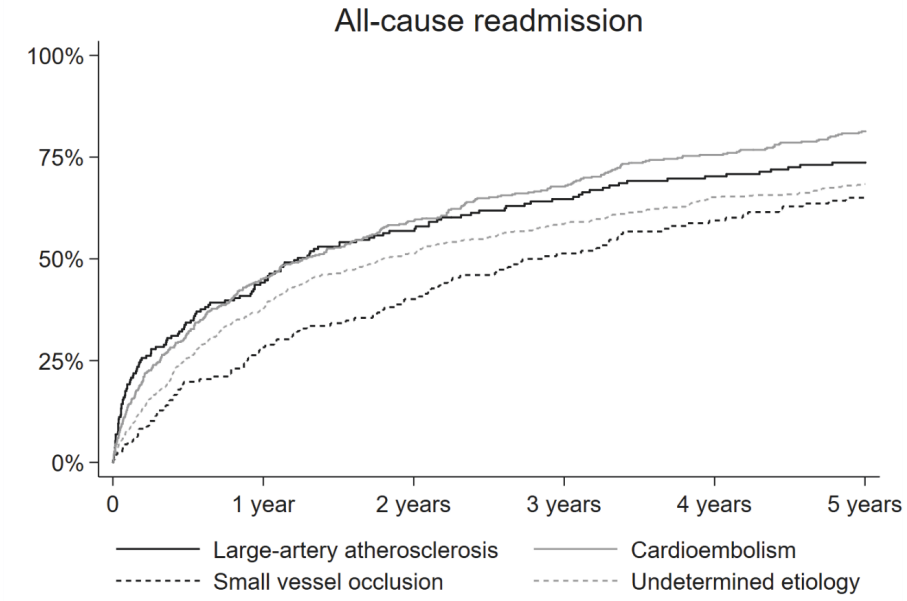

Figure 1. Kaplan Meier failure curves showing incidence estimates of all-cause readmission within 5 years after ischemic stroke or TIA distributed by stroke subtype.

The most common cause of readmission was infection (30%), followed by cardiac disease (20%), stroke-related event (15%), recurrent stroke (14%), and fracture (12%). The incidence of readmission due to infection, cardiac disease, and fractures varied significantly among the stroke subtypes (Figure 2A-C). After adjusting for age, sex, mRS score, premorbid care-status and risk factor burden, CE subtype had a 75% higher risk of readmission due to cardiac disease compared to patients with other stroke subtypes (HR=1.75, 95% CI 1.35-2.25, p<0.001), whereas the risk was 23% lower in patients with SUE (HR=0.77, 95%CI 0.59-0.99, p=0.046). No stroke subtype was significantly associated with infection or fractures in the multivariate analyses (Supplementary Table S1).

There were no significant differences between stroke subtypes in readmission due to recurrent stroke (Figure 2D), stroke-related events (Figure 2E), seizures, venous thromboembolism or gastrointestinal hemorrhage between the stroke subtypes (Supplementary Table S1). Readmission due to ICH varied significantly among stroke subtypes, with the highest incidence in patients with SVO (4.0%).

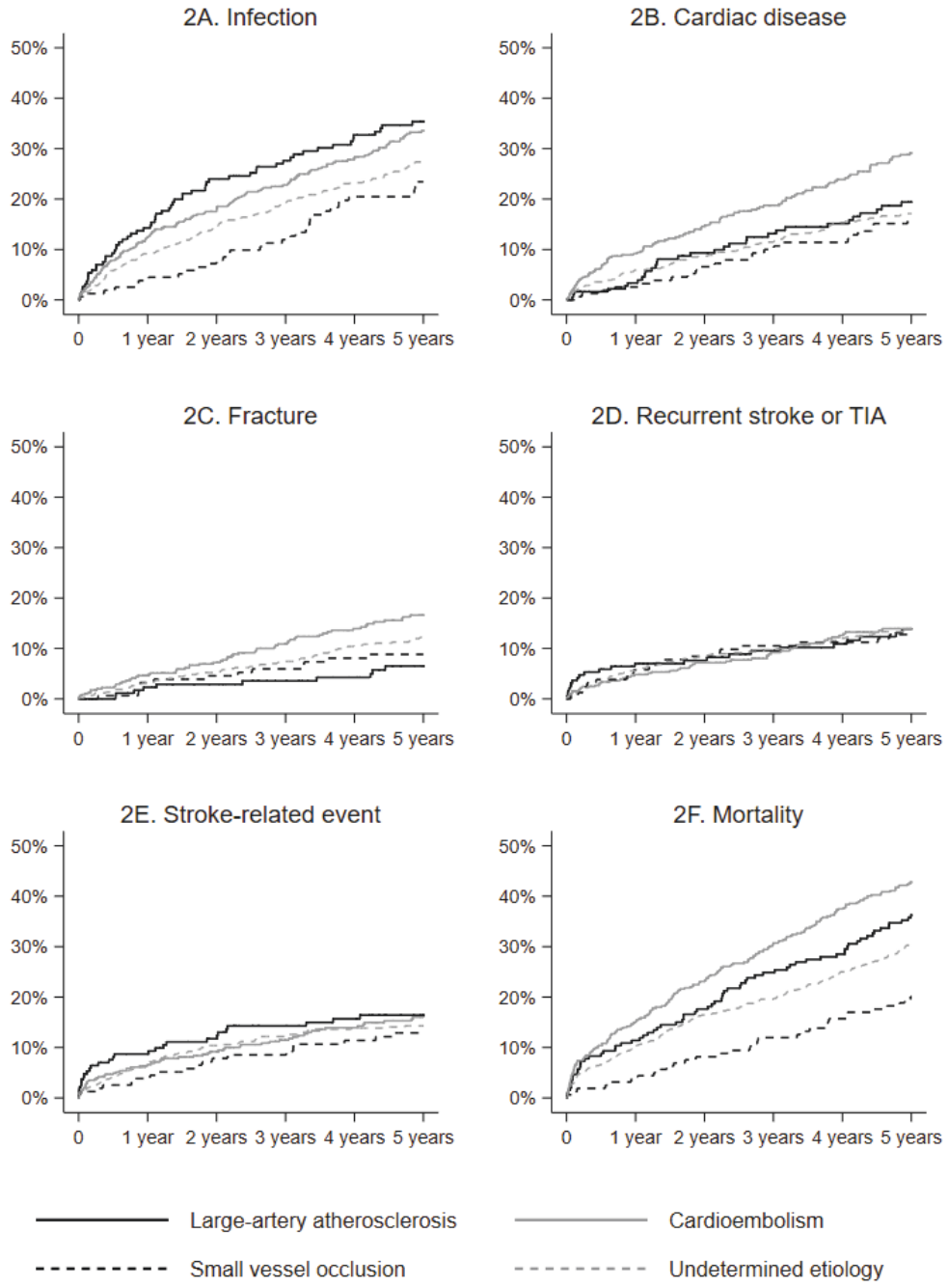

Figure 2. Kaplan Meier failure curves showing incidence estimates of outcome events within five years after ischemic stroke or TIA distributed by stroke subtype for readmission due to infection (A), readmission due to cardiac disease (B), readmission due to fractures (C), recurrent stroke or TIA (D), stroke-related event (E), and mortality (F).

After five years, 404 (40.1%) of the readmitted patients were dead compared to 88 (19.7%) of patients that had not been readmitted (p<0.001). The five-year mortality varied significantly between the stroke subtypes, with the highest mortality observed in patients with CE (Figure 2F). After adjusting for age, sex, mRS score, premorbid care-status and risk factor burden, CE subtype had a 34% higher risk of death within 5 years (HR=1.34, 95% CI 1.12-1.61, p=0.002), and SVO had a 48% lower risk of death (HR=0.52, 95% CI 0.36-0.74, p<0.001).

The Kaplan-Meier incidence estimates of all-cause and cause-specific readmission were almost identical although marginally overestimated for both the cohort as a whole and for each stroke subtype compared to estimates obtained from the survival model that accounted for the competing risk of death (Supplementary Table S2). Exclusion of SOE in all analyses did not alter the demonstrated differences in incidences of all-cause and cause-specific readmissions among the other stroke subtypes.

Discussion

Our study demonstrates that five-year readmission after ischemic stroke or TIA varies depending on the stroke subtype, with incidences ranging from 55% for patients with SOE to 81% for patients with CE. Similar to another Norwegian study, 69% of all patients were readmitted within five years.[8] This is lower than the 83% found in a study from the US,[2] but the distribution of readmission causes were similar to other studies, with infections, cardiac disease, recurrent stroke, and stroke-related events as leading events.[2, 3, 6, 8]

Patients with CE subtype had a significantly increased risk of all-cause readmission compared to other subtypes. This is consistent with findings from a study on stroke patients aged 45 to 64.[19] We also found that SVO subtype had a decreased risk of readmission. The five-year risk of mortality was also significantly higher in patients with CE and lower in patients with SVO, and the incidences of five-year readmission for the stroke subtypes followed the five-year mortality, as both were highest for CE, followed by LAA, SUE, SVO and SOE in descending order. Common risk factor between post-stroke readmission and death could be the cause of this pattern, but readmission may mediate the risk of death after stroke.[20] This implies that careful follow-up and adequate secondary prevention may be important to reduce both post-stroke readmissions and mortality.

CE subtype had the highest occurrence of readmissions due to cardiac disease, a finding which likely relates to underlying cardiac pathology in these patients. Patients with SUE had a lower risk of readmission due to cardiac disease. We have not distinguished between subgroups of SUE, but a possible explanation could be that a high proportion of these patients had cryptogenic stroke, which possibly have a lower occurrence of cardiac disease and vascular risk factors both at the index admission and after discharge.[11]

The five-year incidence of recurrent stroke or TIA was 14%. A recent study found that 16.5% suffered a recurrent stroke or TIA within five years after minor stroke or TIA, whereas a meta-analysis found a pooled 5-year recurrence-risk of 26%.[21, 22] Different five-year recurrence rates might be caused by a decreasing incidence of recurrent stroke,[21] but also study design, study population, and use of secondary preventive treatment. We found no differences in the incidence or risk of recurrent stroke between the stroke subtypes. LAA subtype have an increased risk of early stroke recurrence, but the long-term risk seems to be equal for all stroke subtypes.[12, 23] SVO subtype had a four-fold higher incidence of intracerebral hemorrhage. This might be due to the high occurrence of hypertension and the underlying pathology in small brain vessels that also can lead to hemorrhagic strokes.[11, 24]

Infection was the most common cause of readmission in our study. Severe strokes and increased disability are associated with infections.[25] The median NIHSS score and mRS score was unusually low in our study, a trend which resonates in the Norwegian stroke registry covering 86% of all Norwegian stroke patients.[26] This might be caused by a high awareness of stroke symptoms as results of population-based campaigns and a low threshold for hospital readmission. Readmission with infection varied significantly between the subtypes, with higher incidences for LAA and CE. Functional disability, cardiovascular risk factors, age and sex are known predictors of post-stroke infection, but we found no differences between the stroke subtypes in the risk of readmission with infection after controlling for these factors.[25, 27] The demonstrated differences in the incidence of post-stroke infection is likely due to other factors than the subtype itself.

We found significant variations in the incidence of fractures among the stroke subtypes, with the highest incidence observed in patients with CE subtype, and the lowest in LAA subtype. However, no subtype was associated with fractures after adjustment. The varying incidence of fractures among the stroke subtypes might be influenced by differences in factors associated with post-stroke falls and fractures, such as age, sex, stroke severity, functional outcome,

medications and underlying diseases like atrial fibrillation and osteoporosis.[28, 29] Identification of patients at high risk of falls and fractures is important, as both events could be prevented. Prevention of falls and fractures require multifactorial risk assessment and simultaneous management with exercise to improve mobility and prevent increased bone resorption.

Stroke patients are more often readmitted than matched cohorts without stroke.[2] Prevention of new diseases and readmissions is important for reducing the burden of stroke. Secondary prevention in stroke patients mainly aims at reducing recurrent strokes and cardiovascular disease, but our study demonstrates that non-vascular diseases are prevalent in stroke patients. It also contributes with information which may be helpful for health care providers in determining the risk of new diseases after stroke with information that is easy accessible in a clinical setting.

A limitation to our study is the lack of information on medications and follow-up received after discharge. Some readmissions may not have been accounted for if patients were readmitted to hospitals outside the area of the Western Norwegian Regional Health authorities. Stroke of undetermined etiology represented a high proportion of our cohort despite extensive evaluations, and the study was observational. Thus, we cannot conclude that there is a direct causative relationship between stroke subtype and readmissions. The generalizability of our study is limited by the single-hospital design with patients recruited from a stroke unit, which might reduce the risk of readmission in our population. The strength of our study is the relatively large study population investigated according to a predefined protocol, and the confirmation of readmission and diagnoses by review of medical records.

Conclusions

Within five years, a majority of our patients who survived the hospitalization for ischemic stroke or TIA were readmitted. Infections, stroke-related events, recurrent strokes, cardiac diseases and fractures were the most frequent causes of readmission. Both the incidences of all-cause readmission, cause-specific readmission and mortality depended on the stroke subtype, emphasizing the need for tailored treatment and handling of patients according to the etiology of their ischemic event to reduce the risk of readmissions.

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Supplementary Table S1. Risk of 30-day Unplanned Readmission for Different Causes by Stroke Subtype

Cause of readmission	LAA n=193	CE n=473	SVO n=159	SUE n=608
Death	1.09 (0.84-1.41)	1.34 (1.12-1.61)**	0.52 (0.36-0.74)**	0.91 (0.75-1.09)
Readmission, total	0.98 (0.81-1.18)	1.25 (1.09-1.43)**	0.79 (0.64-0.98)*	0.90 (0.79-1.03)
Recurrent stroke/TIA	0.85 (0.54-1.34)	0.99 (0.71-1.37)	1.07 (0.66-1-74)	1.07 (0.78-1.45)
Stroke-related events	1.28 (0.85-1.92)	1.04 (0.76-1.42)	0.81 (0.50-1.31)	0.94 (0.70-1.26)
Heart disease	0.72 (0.49-1.05)	1.75 (1.35-2.25)**	0.76 (0.49-1.18)	0.77 (0.59-0.99)*
Infection	1.20 (0.90-1.60)	1.11 (0.89-1.37)	0.71 (0.50-1.02)	0.94 (0.77-1.17)
Fractures	0.52 (0.27-1.00)	1.32 (0.94-1.85)	0.86 (0.48-1.53)	1.01 (0.73-1.42)

*$P < 0.05$.
** $P < 0.01$

Supplementary Table S2. Age-adjusted Fine-Gray model of incidences estimates of all-cause and cause-specific readmission within 5 years after ischemic stroke or TIA

	Incidence rates %					
	Total N=1453	LAA N=193	CE N=473	SVO N=159	SOE N=20	SUE N=608
All-cause readmission	69.5	71.0	75.7	62.3	55.3	66.2
Recurrent stroke	11.8	11.7	10.9	11.9	17.0	12.1
IS	9.6	9.0	9.2	8.7	17.0	9.7
ICH	1.1	0.3	1.2	3.8	0.0	0.5
TIA	1.6	2.6	0.7	0.0	0.0	2.5
Stroke-related event	13.0	14.6	12.8	11.9	11.8	12.7
Seizure	3.6	2.8	5.0	1.3	1.2	3.3
Cardiac disease	17.1	16.0	22.8	13.6	1.2	14.5
MI	5.3	6.6	4.8	4.1	1.2	5.6
Arrhythmia	6.6	5.2	9.1	5.5	0.0	3.3
Heart failure	3.6	1.2	6.3	0.7	0.0	3.3
Other	4.9	5.1	6.5	3.1	0.0	4.1
Infection	27.3	30.3	27.2	20.7	8.6	23.1
Pneumonia	11.5	12.9	14.6	7.5	1.2	10.3
UTI	6.3	7.9	4.2	7.6	0.0	6.7
Sepsis	3.6	7.2	3.4	2.5	0.0	3.1
Other	7.9	8.4	8.7	6.5	2.2	7.5
Fracture	8.8	4.8	12.6	4.6	0.0	8.5
Hip fracture	4.0	0.8	6.5	1.8	0.0	3.9
Other	5.0	3.6	6.9	2.5	0.0	4.6
VTE	0.9	1.3	0.9	0.7	1.2	0.6
GI hemorrhage	3.4	3.5	3.4	4.0	0.0	3.3
Other diagnosis	40.5	44.5	43.7	36.4	22.5	38.2

IS, ischemic stroke; TIA, transient ischemic attack; LAA, large artery atherosclerosis; CE, cardioembolism; SVO, small vessel occlusion; SOE, stroke of other determined etiology; SUE, stroke of undetermined etiology; ICH, intracerebral hemorrhage; UTI, urinary tract infection; MI, myocardial infarction; VTE, venous thromboembolism; GI, gastrointestinal.

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